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(54) **9-[(substituted glycyl)amido]-6-demethyl-6-deoxytetracyclines as antibiotic agents**

9-[(Substituierte Glycyl)amido]-6-demethyl-6-deoxytetracycline als antibiotische Mittel

9-[(glycyl substitué)amido]-6-démethyl-6-déoxytétracyclines comme agents antibiotiques

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(56) References cited:
US-A- 3 226 436
US-A- 3 338 963
US-A- 3 579 579

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Description

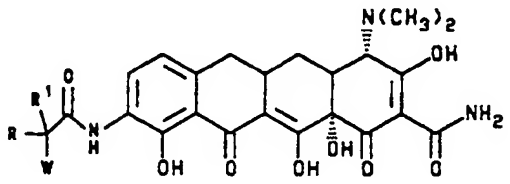
1. Field of the Invention

[0001] The invention relates to novel [4S-(4alpha, 12aalpha)]-4-(dimethylamino)-9-[[(substituted amino)-substituted] amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamides herein after called 9-[(substituted glycyl)-amido]-6-demethyl-6-deoxytetracyclines, which exhibit antibiotic activity against a wide spectrum of organisms including organisms which are resistant to tetracyclines and are useful as antibiotic agents.

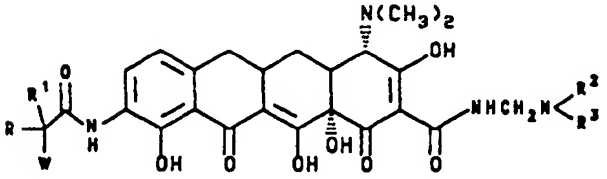
[0002] The invention also relates to novel 9-[(haloacyl)amido]-6-demethyl-6-deoxytetracycline intermediates useful for making the novel compounds of the present invention and to novel methods for producing the novel compounds and intermediate compounds.

SUMMARY OF THE INVENTION

[0003] This invention is concerned with novel 9-[(substituted glycyl)amido]-6-demethyl-6-deoxytetracyclines represented by formula I and II, which have antibacterial activity; with methods of treating infectious diseases in warm blooded animals employing these new compounds; with pharmaceutical preparations containing these compounds; with novel intermediate compounds and processes for the production of these compounds. More particularly, this invention is concerned with compounds of formula I and II which have enhanced in vitro and in vivo antibacterial activity against tetracycline resistant strains as well as a high level of activity against strains which are normally susceptible to tetracyclines.



I



II

[0004] In formula I and II,

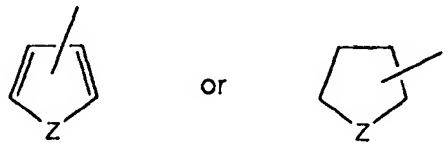
R is selected from hydrogen; straight or branched (C_1-C_8)alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; a-mercapto(C_1-C_4)alkyl group selected from mercaptomethyl, α-mercaptoethyl, α-mercapto-1-methylethyl, α-mercaptopropyl and α-mercaptobutyl; α-hydroxy(C_1-C_4)alkyl group selected from hydroxymethyl, α-hydroxyethyl, α-hydroxy-1-methylethyl, α-hydroxypropyl and α-hydroxybutyl; carboxyl(C_1-C_8) alkyl group; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl and β-naphthyl; substituted(C_6-C_{10})aryl group (substitution selected from hydroxy, halogen, (C_1-C_4)alkoxy, trihalo(C_1-C_3) alkyl, nitro, amino, cyano, (C_1-C_4)alkoxycarbonyl, (C_1-C_3)alkylamino and carboxy); (C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; substituted(C_7-C_9)aralkyl group [substitution selected from halo, (C_1-C_4)alkyl, nitro, hydroxy, amino, mono- or di-substituted (C_1-C_4)alkylamino, (C_1-C_4)alkoxy, (C_1-C_4)alkylsulfonyl, cyano and carboxy] ;

R^1 is selected from hydrogen and (C_1-C_6)alkyl selected from methyl, ethyl propyl, isopropyl, butyl, isobutyl, pentyl and hexyl;
when R does not equal R^1 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D);
W is selected from amino; hydroxylamino; (C_1-C_{12}) straight or branched alkyl monosubstituted amino group substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1-methyl-1-ethylpropyl, heptyl, octyl, nonyl, decyl, undecyl and dodecyl and the diastereomers and enantiomers of said branched alkyl monosubstituted amino group; (C_3-C_8)cycloalkyl monosubstituted amino group substitution selected from cyclopropyl, trans-1,2-dimethylcyclopropyl, cis-1,2-dimethylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]hept-2-yl, and bicyclo[2.2.2]oct-2-yl and the diastereomers and enantiomers of said (C_3-C_8)cycloalkyl monosubstituted amino group; [(C_4-C_{10})cycloalkyl]alkyl monosubstituted amino group substitution selected from (cyclopropyl)methyl, (cyclopropyl)ethyl, (cyclobutyl)methyl, (trans-2-methylcyclopropyl)methyl, and (cis-2-methylcyclobutyl)methyl; (C_3-C_{10}) alkenyl monosubstituted amino group substitution selected from allyl, 3-butenyl, 2-butenyl (cis or trans), 2-pentenyl, 4-octenyl, 2,3-dimethyl-2-butenyl, 3-methyl-2-butenyl 2-cyclopentenyl and 2-cyclohexenyl; (C_6-C_{10})aryl monosubstituted amino group substitution selected from phenyl and naphthyl; (C_7-C_{10})aralkylamino group substitution selected from benzyl, 2-phenylethyl, 1-phenylethyl, 2-(naphthyl)methyl, 1-(naphthyl)methyl and phenylpropyl; substituted (C_6-C_{10})aryl monosubstituted amino group [substitution selected from (C_1-C_5)acyl, (C_1-C_5)acylamino, (C_1-C_4)alkyl, mono or disubstituted (C_1-C_8)alkylamino, (C_1-C_4)alkoxy, (C_1-C_4)alkoxycarbonyl, (C_1-C_4)alkylsulfonyl, amino, carboxy, cyano, halogen, hydroxy, nitro and trihalo(C_1-C_3)alkyl] ; straight or branched symmetrical disubstituted (C_2-C_{14})alkylamino group substitution selected from dimethyl, diethyl, diisopropyl, di-n-propyl, di-n-butyl and diisobutyl; symmetrical disubstituted (C_3-C_{14})cycloalkylamino group substitution selected from dicyclopropyl, dicyclobutyl, dicyclopentyl, dicylohexyl and dicycloheptyl; straight or branched unsymmetrical disubstituted (C_3-C_{14})alkylamino group wherein the total number of carbons in the substitution is not more than 14; unsymmetrical disubstituted (C_4-C_{14})cycloalkylamino group wherein the total number of carbons in the substitution is not more than 14; (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)azacycloalkyl group substitution selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, 4-methylpiperidinyl, 2-methylpyrrolidinyl, cis-3,4-dimethylpyrrolidinyl,
trans-3,4-dimethylpyrrolidinyl,
2-azabicyclo[2.1.1]hex-2-yl,
5-azabicyclo[2.1.1]hex-5-yl,
2-azabicyclo[2.2.1]hept-2-yl,
7-azabicyclo[2.2.1]hept-7-yl, and
2-azabicyclo[2.2.2]oct-2-yl and the diastereomers and enantiomers of said (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)azacycloalkyl group; 1-azaoxacycloalkyl group selected from morpholinyl and 1-aza-5-oxocycloheptane; substituted 1-azaoxacycloalkyl group substitution selected from 2-(C_1-C_3)alkylmorpholinyl,
3-(C_1-C_3)alkylisooxazolidinyl, tetrahydrooxazinyl and 3,4-dihydrooxazinyl; [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group selected from piperazinyl, 2-(C_1-C_3)alkylpiperazinyl, 4-(C_1-C_3)alkylpiperazinyl, 2,4-dimethylpiperazinyl,
4-(C_1-C_4)alkoxypiperazinyl, 4-(C_6-C_{10})aryloxypiperazinyl, 4-hydroxypiperazinyl, 2,5-diazabicyclo[2.2.1]hept-2-yl, 2,5-diaza-5-methylbicyclo[2.2.1]hept-2-yl, 2,3-diaza-3-methylbicyclo[2.2.2]oct-2-yl, and 2,5-diaza-5,7-dimethylbicyclo [2.2.2]oct-2-yl and the diastereomers or enantiomers of said [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group; 1-azathiacycloalkyl and substituted 1-azathiacycloalkyl group selected from thiomorpholinyl, 2-(C_1-C_3)alkylthiomorpholinyl and 3-(C_3-C_6)cycloalkylthiomorpholinyl; N-azolyl and substituted N-azolyl group selected from 1-imidazolyl, 2-(C_1-C_3)alkyl-1-imidazolyl, 3-(C_1-C_3)alkyl-1-imidazolyl, 1-pyrrolyl, 2-(C_1-C_3)alkyl-1-pyrrolyl, 3-(C_1-C_3)alkyl-1-pyrrolyl, 1-pyrazolyl, 3-(C_1-C_3)-alkyl-1-pyrazolyl, indolyl, 1-(1,2,3-triazolyl), 4-(C_1-C_3)alkyl-1-(1,2,3-triazolyl), 5-(C_1-C_3)alkyl-1-(1,2,3-triazolyl), 4-(1,2,4-triazolyl, 1-tetrazolyl, 2-tetrazolyl and benzimidazolyl; (heterocycle)amino group said heterocycle selected from 2- or 3-furanyl, 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2- or 5-pyridazinyl, 2-pyrazinyl, 2-(imidazolyl), (benzimidazolyl), and (benzothiazolyl) and substituted (heterocycle)amino group (substitution selected from straight or branched (C_1-C_6)alkyl) ; (heterocycle)methylamino group selected from 2- or 3-furylmethylamino, 2- or 3-thienylmethylamino, 2-, 3- or 4-pyridylmethylamino, 2- or 5-pyridazinylmethyl- amino, 2-pyrazinylmethylamino, 2-(imidazolyl)methyl- amino, (benzimidazolyl)methylamino, and (benzothiazolyl)methylamino and substituted (heterocycle)methylamino group (substitution selected from straight or branched (C_1-C_6)alkyl); carboxy (C_2-C_4)alkylamino group selected from aminoacetic acid, α-aminopropionic acid, β-aminopropionic acid, α-butyric acid, and β-aminobutyric acid and the enantiomers of said carboxy(C_2-C_4)alkylamino group; (C_1-C_4)alkoxycarbonylamino group substitution selected from methoxycarbonyl, ethoxycarbonyl, allyloxycarbonyl, propoxycarbonyl, isoproproxycarbonyl, 1,1-dimethyl- ethoxycarbonyl, n-butoxycarbonyl, and 2-methylpropoxycarbonyl; (C_1-C_4) alkoxyamino group substitution selected from methoxy, ethoxy.n-propoxy, 1-methylethoxy, n-butoxy, 2-methylpropoxy, and 1,1-dimethylethoxy; (C_3-C_8)cy-

cloalkoxyamino group selected from cyclopropoxy, trans-1,2-dimethylcyclo-propoxy, cis-1,2-dimethylcyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, cycloheptoxy, cyclooctoxy, bicyclo[2.2.1]hept-2-yloxy, and bicyclo[2.2.2]oct-2-yloxy and the diastereomers and enantiomers of said (C_3-C_8)cycloalkoxyamino group; (C_6-C_{10})aryloxyamino group selected from phenoxyamino, 1-naphthyloxyamino and 2-naphthyloxyamino; (C_7-C_{11}) arylalkoxyamino group substitution selected from benzyloxy, 2-phenylethoxy, 1-phenylethoxy, 2-(naphthyl)methoxy, 1-(naphthyl)- methoxy and phenylpropoxy;

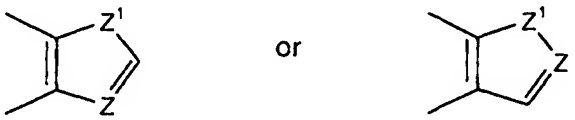
R^2 and R^3 are independently selected from

(i) hydrogen providing that R^2 and R^3 are not both hydrogen;
(ii) straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl;
(iii) (C_6-C_{10})aryl group selected from phenyl, α-naphthyl or β-naphthyl;
(iv) (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl;
(v) a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



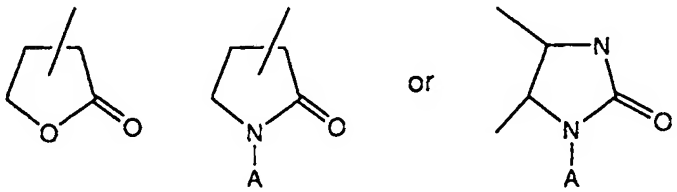
Z = N, O, S or Se

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl;
(vi) a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



Z or Z^1 = N, O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl, or
(vii) a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(wherein A is selected from hydrogen; straight or branched (C_1-C_4)alkyl; C_6-aryl; substituted C_6-aryl (substitution selected from halo,(C_1-C_4)alkoxy, trihalo(C_1-C_3)alkyl, nitro, amino, cyano, (C_1-C_4)-alkoxycarbonyl, (C_1-C_3)

alkylamino or carboxy); benzyl. 1-phenylethyl. 2-phenylethyl or phenylpropyl) such as γ-butyrolactam, γ-butyrolactone. imidazolidinone or N-aminoimidazolidinone. or a six membered aromatic ring with one to three N heteroatoms such as pyridyl, pyridazinyl, pyrazinyl. sym-triazinyl. unsymtriazinyl, pyrimidinyl or (C_1-C_3) alkylthiopyridazinyl, or a six membered saturated ring with one or two N. O. S or Se heteroatoms and an adjacent appended O heteroatom such as 2.3-dioxo-1-piperazinyl, 4-ethyl-2.3-dioxo-1-piperazinyl, 4-methyl-2.3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1-piperazinyl, 2-dioxomorpholinyl. 2-dioxo-thiomorpholinyl;
(viii) or a six membered aromatic ring with one to three N heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtriazinyl, unsym-triazinyl, pyrimidinyl or (C_1-C_3)alkylthiopyridazinyl;
(ix) a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1- piperazinyl, 4-cyclopropyl-2-dioxo-1-piperazinyl, 2-dioxomorpholinyl, 2-dioxothiomorpholinyl;
(x) -$(CH_2)_n$COOR^4 where n=0-4 and R is selected from hydrogen; straight or branched (C_1-C_3)alkyl selected from methyl, ethyl, n-propyl or 1-methylethyl;
(xi) (C_6-C_{10})aryl selected from phenyl, α-naphthyl or β-naphthyl;

or R and R^3 taken together are:

(i) -$(CH_2)_2B(CH_2)_2$-, wherein B is selected from $(CH_2)_n$ and n=0-1, -NH, -N(C_1-C_3)alkyl [straight or branched], -N(C_1-C_4)alkoxy, oxygen, sulfur or
(ii) substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

[0005] This invention also provides the following compounds:

[7S-(7alpha, 10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1, 8, 10a, 11-tetrahydroxy-10, 12dioxo-2-naphthacenyl]-4-ethyl-lH-pyrazole-1-acetamide, **(Formula I, R and R^1 = H, W = 4-ethyl-1H-pyrazol-1-yl);**
14S-(4alpha, 12aalpha)] -4-(Dimethylamino)-1, 4, 4a, 5, 5a, 6, 11, 12a-octahydro-3, 10, 12, 12a-tetrahydroxy-1, 11-dioxo-9-[[[methyl(phenylmethyl)amino]acetyl]amino]-2-naphthacenecarboxamide,**(Formula I, R and R^1 = H, W = N-methylbenzylamino);**
[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a, 11tetrahydroxy-10,12dioxo-2-naphthacenyl]-6-methyl-2-azabicyclo[2.2.2]octane-2-acetamide, **(Formula I, R and R^1 = H, W = 6-methyl-2-azabicyclo[2.2.2]octan-2-yl) ;**
[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[[(2-methylcyclopropyl)oxy]amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R and R^1 = H, W = (2-methylcyclopropyl)-oxyamino);**
[7S-(7alpha, 10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a, 11-tetrahydroxy-10,12dioxo-2-naphthacenyl]-3-ethyl-1-pyrrolidineacetamide, **(Formula I, R and R^1 = H, W = 3-ethylpyrrolidin-1-yl) ;**
[7S-(7alpha, 10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a, 11-tetrahydroxy-10,12dioxo-2-naphthacenyl]-4-(aminomethyl)-α-methyl-1-piperidineacetamide, **(Formula I, R = CH$_3$, R^1 = H, W = 4- aminomethylpiperidn-1-yl);**
[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[2-[[(3-methylcyclobutyl)oxy]amino]-1-oxobutyl]amino]-1,11-dioxo-2-naphthacenecarboxamide hydrobromide, **(Formula I, R = H, R^1 = Et, W = 3-methylcyclobutyloxyamino);**
[7S-(7alpha,10aalpha)] -N-[9-(Aminocarbonyl) -7-(dimethylamino) -5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a, 11-tetrahydroxy-10,12dioxo-2-naphthacenyl]-- -ethyl-4-methyl-2-isoxazolidineacetamide, **(Formula I, R = Et, R^1 = H, W = 4-methyl-isoxazolidin-2-yl) ;**
[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a, 11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-a-ethyl-3-methyl-4H-1,2,4-triazole-4-acetamide, **(Formula I, R = Et, R^1 = H, W = 3-methyl-4H-1,2,4-triazol-4-yl) ;**
or
[7S-(7alpha, 10aalpha)]-4-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a, 11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-3-[ethyl(phenylmethyl)amino]-4-oxobutanoic acid **(Formula I, R = carboxymethyl, R^1 = H, W = N-ethylbenzylamino).**

[0006] Preferred compounds are compounds according to the above formula I and II wherein:
R is selected from hydrogen; straight or branched (C_1-C_8)alkyl group selected from methyl, ethyl, propyl, isopropyl,

butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α-mercapto(C_1-C_4)alkyl group selected from mercaptomethyl, α-mercaptoethyl, α-mercapto-1-methylethyl, α-mercaptopropyl and α-mercaptobutyl; α-hydroxy(C_1-C_4)alkyl group selected from hydroxymethyl, α-hydroxyethyl, α-hydroxy-1-methylethyl, α-hydroxypropyl and α-hydroxybutyl; carboxyl(C_1-C_8) alkyl group; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl and β-naphthyl; (C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl;

substituted(C_7-C_9)aralkyl group [substitution selected from halo, (C_1-C_4)alkyl, nitro, hydroxy, amino, mono-or di-substituted (C_1-C_4)alkylamino, (C_1-C_4)alkoxy, (C_1-C_4)alkylsulfonyl, cyano and carboxy];

R^1 is selected from hydrogen and (C_1-C_6)alkyl selected from methyl, ethyl propyl, isopropyl, butyl, isobutyl, pentyl and hexyl;

when R does not equal R^1 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the W substituent) maybe either the racemate (DL) or the individual enantiomers (L or D);

W is selected from amino; hydroxylamino; (C_1-C_{12}) straight or branched alkyl monosubstituted amino group substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, l-methyl-l-ethylpropyl, heptyl, octyl, nonyl, decyl, undecyl and dodecyl and the diastereomers and enantiomers of said branched alkyl monosubstituted amino group; (C_3-C_8)cycloalkyl monosubstituted amino group substitution selected from cyclopropyl, trans-1,2-dimethylcyclopropyl, cis-1,2-dimethylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]hept-2-yl, and bicyclo[2.2.2]oct-2-yl and the diastereomers and enantiomers of said (C_3-C_8)cycloalkyl monosubstituted amino group; [(C_4-C_{10})cycloalkyl]alkyl monosubstituted amino group substitution selected from (cyclopropyl)methyl, (cyclopropyl)ethyl, (cyclobutyl)methyl, (trans-2-methylcyclopropyl)methyl, and (cis-2-methylcyclobutyl)methyl; (C_3-C_{10}) alkenyl monosubstituted amino group substitution selected from allyl, 3-butenyl, 2-butenyl (cis or trans), 2-pentenyl, 4-octenyl, 2,3-dimethyl-2-butenyl, 3-methyl-2-butenyl 2-cyclopentenyl and 2-cyclohexenyl; (C_6-C_{10})aryl monosubstituted amino group substitution selected from phenyl and naphthyl; (C_7-C_{11})aralkylamino group substitution selected from benzyl, 2-phenylethyl, 1-phenylethyl, 2-(naphthyl)methyl, 1-(naphthyl)methyl and phenylpropyl; straight or branched symmetrical disubstituted (C_2-C_{14})alkylamino group substitution selected from dimethyl, diethyl, diisopropyl and di-n-propyl; symmetrical disubstituted (C_3-C_{14})cycloalkylamino group substitution selected from dicyclopropyl, dicyclobutyl, dicyclopentyl, dicylohexyl and dicycloheptyl; straight or branched unsymmetrical disubstituted (C_3-C_{14}) alkylamino group wherein the total number of carbons in the substitution is not more than 14; unsymmetrical disubstituted (C_4-C_{14})cycloalkylamino group wherein the total number of carbons in the substitution is not more than 14; (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)azacycloalkyl group selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, 4-methylpiperidinyl, 2-methylpyrrolidinyl, cis-3,4-dimethylpyrrolidinyl, trans-3,4-dimethylpyrrolidinyl, 2-azabicyclo [2.1.1]hex-2-yl, 5-azabicyclo[2.1.1]hex-5-yl, 2-azabicyclo[2.2.1]hept-2-yl, 7-azabicyclo[2.2.1]hept-7-yl, and 2-azabicyclo[2.2.2]oct-2-yl and the diastereomers and enantiomers of said (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)azacycloalkyl group; 1-azaoxacycloalkyl group selected from morpholinyl and 1-aza-5-oxacycloheptane; substituted 1-azaoxacycloalkyl group selected from 2-(C_1-C_3)alkylmorpholinyl, 3-(C_1-C_3)alkylisoxazolidinyl, tetrahydrooxazinyl and 3,4-dihydrooxazinyl; [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group selected from piperazinyl, 2-(C_1-C_4)alkylpiperazinyl, 4-(C_1-C_3)alkylpiperazinyl, 2,4-dimethylpiperazinyl, 4-(C_1-C_3)alkoxypiperazinyl, 4-(C_6-C_{10})-aryloxypiperazinyl, 4-hydroxypiperazinyl, 2,5-diaza-bicyclo[2.2.1]hept-2-yl, 2,5-diaza-5-methylbicyclo-[2.2.1]hept-2-yl, 2,3-diaza-3-methylbicyclo[2.2.2]-oct-2-yl, and 2,5-diaza-5,7-dimethylbicyclo[2.2.2]oct-2-yl and the diastereomers or enantiomers of said [1,n]-diazacycloalkyl and substituted [1,n]-diaza-cycloalkyl group; 1-azathiacycloalkyl and substituted 1-azathiacycloalkyl group selected from thiomorpholinyl, 2-(C_1-C_3)alkylthiomorpholinyl and 3-(C_3-C_6)-cycloalkylthiomorpholinyl; N-azolyl and substituted N-azolyl group selected from 1-imidazolyl, 2-(C_1-C_3)-alkyl-1-imidazolyl, 3-(C_1-C_3)alkyl-1-imidazolyl, 1-pyrrolyl, 2-(C_1-C_3)alkyl-l-pyrrolyl, 3-(C_1-C_3)alkyl-1-pyrrolyl, 1-pyrazolyl, 3-(C_1-C_3) alkyl-l-pyrazolyl, indolyl, 1-(1,2,3-triazo- lyl), 4-alkyl-1-(1,2,3-triazolyl), 5-(C_1-C_3)alkyl-1-(1,2,3-triazolyl), 4-(1,2,4-triazolyl, 1-tetrazolyl, 2-tetrazolyl and benzimidazolyl; (heterocycle)amino group said heterocycle selected from 2- or 3-furanyl, 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2- or 5-pyridazinyl, 2-pyrazinyl, 2-(imidazolyl), (benzimidazolyl), and (benzothiazolyl) and substituted (heterocycle)amino group (substitution selected from straight or branched (C_1-C_6)alkyl); (heterocycle)methylamino group selected from 2- or 3-furylmethylamino, 2- or 3-thienylmethylamino, 2-, 3- or 4-pyridylmethylamino, 2- or 5-pyridazinylmethylamino, 2-pyrazinylmethylamino, 2-(imidazolyl)methylamino, (benzimidazolyl)methylamino, and (benzothiazolyl)methylamino and substituted (heterocycle)methylamino group (substitution selected from straight or branched (C_1-C_6)alkyl); carboxy(C_2-C_4)alkylamino group selected from aminoacetic acid, α-aminopropionic acid, β-aminopropionic acid, α-butyric acid, and β-aminobutyric acid and the enantiomers of said carboxy (C_2-C_4)alkylamino group; (C_1-C_4)alkoxycarbonylamino group substitution selected from methoxycarbonyl, ethoxycarbonyl, allyloxycarbonyl, propoxycarbonyl, isoproproxycarbonyl, 1,1-dimethylethoxycarbonyl, n-butoxycarbonyl, and 2-methylpropoxycarbonyl; (C_1-C_4)alkoxyamino group substitution selected from methoxy, ethoxy,n-propoxy, 1-methyl- ethoxy, n-butoxy, 2-methylpropoxy, and 1,1-dimethylethoxy; (C_3-C_8)-cycloalkoxyamino group substitution selected

from cyclopropoxy, trans-1,2-dimethylcyclopropoxy, cis-1,2-dimethylcyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, cycloheptoxy, cyclooctoxy, bicyclo[2.2.1]hept-2-yloxy, and bicyclo[2.2.2]oct-2- yloxy and the diastereomers and enantiomers of said (C_3-C_8)cycloalkoxyamino group; (C_6-C_{10})aryloxyamino group selected from phenoxyamino, 1-naphthyloxyamino and 2-naphthyloxyamino;
(C_7-C_{11})arylalkoxyamino group substitution selected from benzyloxy, 2-phenylethoxy, 1-phenylethoxy, 2-(naphthyl) methoxy, 1-(naphthyl)- methoxy and phenylpropoxy; R^2 and R^3 are independently selected from:

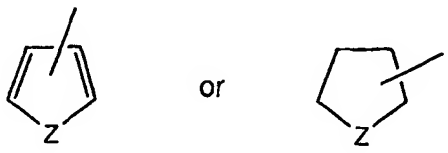
(i) hydrogen providing that R^2 and R^3 are not both hydrogen;

(ii) straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl;

(iii) (C_6-C_{10})aryl group selected from phenyl, α-naphthyl or β-naphthyl;

(iv) (C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl;

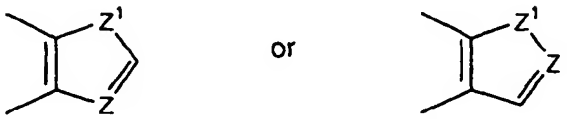
(v) a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



Z = N, O, S or Se

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl,

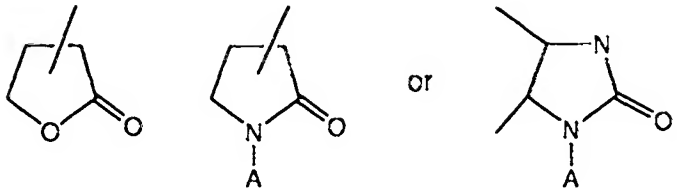
(vi) a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



Z or Z^1 = N, O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl,

(vii) a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (C_1-C_4)alkyl; C_6-aryl; substituted C_6-aryl (substitution selected from halo, (C_1-C_4)alkoxy, trihalo(C_1-C_3)alkyl, nitro, amino, cyano, (C_1-C_4)alkoxycarbonyl, (C_1-C_3)alkylamino or carboxy): (C_7-C_9)-aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl) such as γ-butyrolactam, γ-butyrolactone, imidazolidinone or N-aminoimidazolidinone,

(viii) a six membered aromatic ring with one to three N heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, sym-triazinyl, unsym-triazinyl, pyrimidinyl or (C_1-C_3)alkylthiopyridazinyl,

(ix) a six membered saturated ring
with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1-piperazinyl, 2-dioxomorpholinyl, 2-dioxo-thiomorpholinyl;

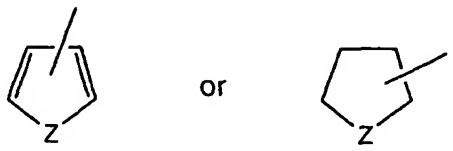
(x) - $(CH_2)_nCOOR^4$ where n=0-4 and R^4 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl;

(xi) or (C_6-C_{10})aryl group selected from phenyl, α-naphthyl, β-naphthyl;

or R^2 and R^3 taken together are-$(CH_2)_2B(CH_2)_2$-, wherein B is selected from $(CH_2)_n$ and n=0-1, -NH, -N(C_1-C_3)alkyl [straight or branched], -N(C_1-C_4)alkoxy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

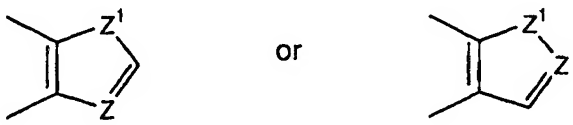
[0007] Particularly preferred compounds are compounds according to the above formula I and II wherein:
R is selected from hydrogen; straight or branched (C_1-C_8)alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α-mercapto(C_1-C_4)alkyl group selected from mercaptomethyl, α-mercaptoethyl, α-mercapto-1-methylethyl and α-mercaptopropyl; α-hydroxy-(C_1-C_4)alkyl group selected from hydroxymethyl, α-hydroxyethyl, α-hydroxy-1-methylethyl and α-hydroxypropyl; carboxyl(C_1-C_8)alkyl group; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl and β-naphthyl; (C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; R^1 is selected from hydrogen and (C_1-C_6)alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl;
when R does not equal R^1 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the W substituent) maybe either the racemate (DL) or the individual enantiomers (L or D);
W is selected from amino; (C_1-C_{12}) straight or branched alkyl monosubstituted amino group substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethyl- ethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1-methyl-1-ethylpropyl, heptyl, octyl, nonyl and decyl and the diastereomers and enantiomers of said branched alkyl monosubstituted amino group; (C_3-C_8)cycloalkyl monosubstituted amino group substitution selected from cyclopropyl, trans-1,2-dimethylcyclopropyl, cis-1,2-dimethylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl and the diastereomers and enantiomers of said (C_3-C_8)cycloalkyl monosubstituted amino group; [(C_4-C_{10})cycloalkyl]alkyl monosubstituted amino group substitution selected from (cyclopropyl)methyl, (cyclopropyl)ethyl and (cyclobutyl)methyl; (C_3-C_{10})alkenyl monosubstituted amino group substitution selected from allyl, 3-butenyl, 2-butenyl (cis or trans), 2-pentenyl, 4-octenyl, 2,3-dimethyl-2-butenyl, 3-methyl-2-butenyl 2-cyclopentenyl and 2-cyclohexenyl; (C_7-C_{10})aralkylamino group substitution selected from benzyl, 2-phenylethyl, 1-phenylethyl, 2-(naphthyl)methyl, 1-(naphthyl)methyl and phenylpropyl; straight or branched symmetrical disubstituted (C_2-C_{14})alkylamino group substitution selected from dimethyl, diethyl, diisopropyl and di-n-propyl; straight or branched unsymmetrical disubstituted (C_3-C_{14})alkylamino group wherein the total number of carbons in the substitution is not more than 14; unsymmetrical disubstituted (C_4-C_{14})cyclo- alkylamino group wherein the total number

of carbons in the substitution is not more than 14;
(C_2-C_8)azacycloalkyl and substituted (C2-C8)azacyclo- alkyl group selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, 4-methylpiperidinyl, 2- methylpyrrolidinyl, cis-3,4-dimethylpyrrolidinyl, and trans-3,4-dimethylpyrrolidinyl and the diastereomers and enantiomers of said (C_2-C_8)azacycloalkyl and sub- stituted (C_2-C_8)azacycloalkyl group;
1-azaoxacycloalkyl group selected from morpholinyl and 1-aza-5-oxacycloheptane; substituted 1-azaoxacyclo- alkyl group selected from 2-(C_1-C_3)alkylmorpholinyl,
3-(C_1-C_3)alkylisooxazolidinyl and tetrahydrooxazinyl; [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group selected from piperazinyl, 2-(C_1-C_3)alkylpiperazinyl,
4-(C_1-C_3)alkylpiperazinyl, 2,4-dimethylpiperazinyl, 4-hydroxypiperazinyl, 2,5-diazabicyclo[2.2.1]hept-2-yl, 2,5-diaza-5-methyl- bicyclo[2.2.1]hept-2-yl, and 2,3-diaza-3-methylbicyclo- [2.2.2]oct-2-yl, the diastereomers or enantiomers of said [1,n]-diazacycloalkyl and substituted [1,n]-diaza- cycloalkyl group; 1-azathiacycloalkyl and substituted 1-azathiacycloalkyl group selected from thiomorpholinyl and 2-(C_1-C_3)alkylthiomorpholinyl; N-azolyl and substituted N-azolyl group selected from 1-imidazolyl, 2-(C_1-C_3)alkyl-1-imidazolyl, 3-(C_1-C_3)alkyl-1-imida-zolyl, 1-pyrrolyl, 2-(C_1-C_3)alkyl-1-pyrrolyl, 3-(C_1-C_3)alkyl-1-pyrrolyl, 1-pyrazolyl, 3-(C_1-C_3)alkyl-1-pyrazolyl, indolyl, 1-(1,2,3-triazo- lyl), 4-(C_1-C_3)alkyl-1-(1,2,3-triazolyl), 5-(C_1-C_3)- alkyl-1-(1,2,3-triazolyl) and 4-(1,2,4-triazolyl; (heterocycle)methylamino group selected from 2- or 3-furylmethylamino, 2- or 3-thienylmethylamino, 2-, 3- or 4-pyridylmethylamino, 2- or 5-pyridazinylmethylamino, 2-pyrazinylmethylamino, 2-(imidazolyl)methyl- amino, (benzimidazolyl)methylamino, and (benzothiazolyl) methylamino and substituted (heterocycle)methyl- amino group (substitution selected from straight or branched (C_1-C_6)alkyl); carboxy(C_2-C_4)alkylamino group selected from aminoacetic acid, α-aminopropionic acid, β-aminopropionic acid, α-butyric acid, and β-aminobutyric acid and the enantiomers of said carboxy(C_2-C_4)alkylamino group;
(C_1-C_4)alkoxycarbonylamino group substitution selected from methoxycarbonyl, ethoxycarbonyl, allyloxycarbonyl, propoxycarbonyl, isoproproxycarbonyl, 1,1-dimethylethoxycarbonyl, n-butoxycarbonyl, and 2-methylpropoxycarbonyl; (C_1-C_4)alkoxyamino group substitution selected from methoxy, ethoxy, n-propoxy, 1-methylethoxy, n-butoxy, 2-methylpropoxy, and 1,1-dimethylethoxy; (C_7-C_{11})arylalkoxyamino group substitution selected from benzyoxy, 2-phenylethoxy, 1-phenylethoxy, 2-(naphthyl)methoxy, 1-(naphthyl)- methoxy and phenylpropoxy; R^2 and R^3 are independently selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



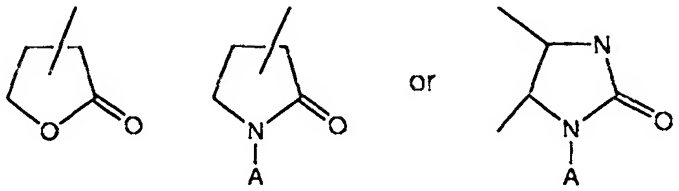
Z = N, O, S or Se

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



Z or Z^1 = N, O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (C_1-C_4)alkyl; C_6-aryl; substituted C_6-aryl (substitution selected from halo, (C_1-C_4)alkoxy, trihalo(C_1-C_3)alkyl, nitro, amino, cyano, (C_1-C_4)-alkoxycarbonyl, (C_1-C_3)alkylamino or carboxy); (C_7-C_9)-aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)
such as γ-butyrolactam, γ-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, sym-triazinyl, unsym-triazinyl, pyrimidinyl or (C_1-C_3) alkylthiopyridazinyl, or a six membered saturated ring
with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-2,3-dioxo-l-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1-piperazinyl, 2-dioxomorpholinyl, 2-dioxo-thiomorpholinyl; or -$(CH_2)_n$COO R^4 where n=0-4 and R^4 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; or (C_6-C_{10})aryl group selected from phenyl, α-naphthyl, β-naphthyl;
or R^2 and R^3 taken together are -$(CH_2)_2B(CH_2)_2$-, wherein B is selected from $(CH_2)_n$ and n=0-1, -NH, -N(C_1-C_3)alkyl [straight or branched], -N(C_1-C_4)alkoxy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate, and the pharmacologically acceptable organic and inorganic salts or metal complexes.

[0008] Compounds of special interest are compounds according to the above formula I and II wherein:

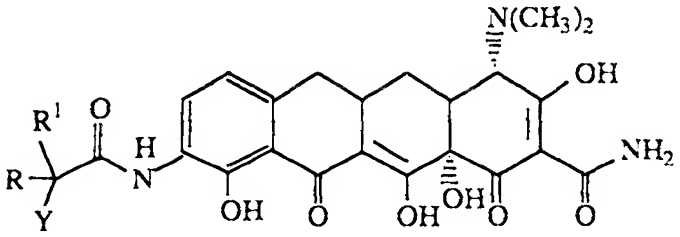
R and R^1 are independently selected from hydrogen, methyl and ethyl; and when R does not equal R^1 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D);

W is selected from amino; (C_1-C_8) straight or branched alkyl monosubstituted amino group substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, n-hexyl and n-octyl; (C_3-C_6)cycloalkyl monosubstituted amino group substitution selected from cyclopropyl, cyclopentyl and cyclohexyl; [(C_4-C_5)cycloalkyl] alkyl monosubstituted amino group substitution selected from (cyclopropyl)methyl and (cyclopropyl)ethyl; (C_3-C_4)alkenyl monosubstituted amino group substitution selected from allyl and 3-butenyl; (C_7-C_{10}) aralkylamino group substitution selected from benzyl, 2-phenylethyl and 1-phenylethyl; straight or branched symmetrical disubstituted (C_2-C_4) alkylamino group substitution selected from dimethyl and diethyl; straight or branched unsymmetrical disubstituted (C_3)alkylamino group substitution selected from methyl(ethyl);
(C_2-C_5)azacycloalkyl group selected from pyrrolidinyl and piperidinyl; 1-azaoxacycloalkyl group selected from morpholinyl; substituted 1-azaoxacycloalkyl group selected from 2-(C_1-C_3)alkylmorpholinyl; [1,n]-diazacycloalkyl and substituted [1,n]-diazacyclo- alkyl group selected from piperazinyl, 2-(C_1-C_3)alkyl- piperazinyl, 4-(C_1-C_3)alkylpiperazinyl, and 2,5-diaza-5-methylbicyclo[2.2.1]hept-2-yl and
the diastereomers and enantiomers of said [1,n]-diaza-cycloalkyl and substituted [1,n]-diazacycloalkyl group; 1-azathiacycloalkyl and substituted 1-azathiacycloalkyl group selected from thiomorpholinyl and
2-(C_1-C_3)alkylthiomorpholinyl; N-azolyl group selected from 1-imidazolyl; (heterocycle)methylamino group selected from 2- or 3-thienylmethylamino and 2-, 3- or 4-pyridylmethylamino; (C_1-C_4)alkoxycarbonylamino group substitution selected from methoxycarbonyl, ethoxycarbonyl, and 1,1-dimethylethoxycarbonyl;

R^2 and R^3 are independently selected from hydrogen, methyl, ethyl, n-propyl or 1-methylethyl with the proviso that R^2 and R^3 cannot both be hydrogen;
or R and R^3 taken together are -

(i) -$(CH_2)_2B(CH_2)_2$-, wherein B is selected from $(CH_2)_n$ and n=0-1, -NH, -N(C_1-C_3)alkyl [straight or branched], -N(C_1-C_4)alkoxy, oxygen, sulfur or
(ii) substituted congeners selected from (L or D)proline and ethyl(L or D)prolinate and the pharmacologically acceptable organic and inorganic salts or metal complexes.

[0009] Also included in the present invention are compounds useful as intermediates for producing the above compounds of formula I and II. Such intermediates include those having the formula III:



(III)

wherein:

Y is selected from bromine, chlorine, fluorine and iodine;

R is selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl, mercaptomethyl, α-mercaptoethyl, α-mercapto-1-methylethyl, α-mercaptopropyl and α-mercaptobutyl, hydroxymethyl, α-hydroxyethyl, α-hydroxy-1- methylethyl, α-hydroxypropyl and α-hydroxybutyl; carboxyl (C_1-C_8) alkyl group; phenyl, α-naphthyl and β-naphthyl group each optionally substituted by hydroxy, halogen, (C_1-C_4)alkoxy, trihalo (C_1-C_3)- alkyl, nitro, amino, cyano, (C_1-C_4)alkoxycarbonyl, (C_1-C_3)alkylamino and carboxy); or a benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl group, each optionally substituted by halo, (C_1-C_4)alkyl, nitro, hydroxy, amino, mono- or di-substituted (C_1-C_4)alkylamino, (C_1-C_4)alkoxy, (C_1-C_4)alkylsulfonyl, cyano and carboxy;

R^1 is selected from hydrogen, methyl, ethyl propyl, isopropyl, butyl, isobutyl, pentyl and hexyl; and when R does not equal R^1 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the Y substituent) may be be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts and metal complexes.

[0010] Preferred compounds are compounds according to the above formula III wherein:

Y is selected from bromine, chlorine, fluorine and iodine;

R is selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α-mercapto (C_1-C_4)alkyl group selected from mercaptomethyl, α-mercaptoethyl, α-mercapto-1-methylethyl, α-mercaptopropyl and α-mercaptobutyl; α-hydroxy(C_1-C_4)alkyl group selected from hydroxymethyl, α-hydroxyethyl, α-hydroxy-1-methylethyl, α-hydroxypropyl and α-hydroxybutyl; carboxyl(C_1-C_8)alkyl group; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl and β-naphthyl; (C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; substituted (C_7-C_9)aralkyl group [substitution selected from halo, (C_1-C_4)alkyl, nitro, hydroxy, amino, mono- or di-substituted (C_1-C_4)alkylamino, (C_1-C_4)alkoxy, (C_1-C_4)alkylsulfonyl, cyano and

R^1 is selected from hydrogen and (C_1-C_6)alkyl selected from methyl, ethyl propyl, isopropyl, butyl, isobutyl, pentyl and hexyl;

And when R does not equal R^1 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the Y substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts and metal complexes.

[0011] Particularly preferred compounds are compounds according to the above formula III wherein:

Y is selected from bromine, chlorine, fluorine and iodine;

R is selected from hydrogen; straight or branched (C_1-C_8)alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α-mercapto(C_1-C_4)alkyl group selected from mercaptomethyl, α-mercaptoethyl, α-mercapto-1-methylethyl and α-mercaptopropyl; α-hydroxy-(C_1-C_4)alkyl group selected from hydroxymethyl, α-hydroxyethyl, α-hydroxy-1-methylethyl and α-hydroxypropyl; carboxyl(C_1-C_8)alkyl group; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl and β-naphthyl; (C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; R^1 is selected from hydrogen and (C_1-C_6)alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl; when R does not equal R^1 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the Y substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts and metal complexes.

[0012] Compounds of special interest are compounds according to the above formula III wherein:

Y is selected from bromine, chlorine, fluorine and iodine;

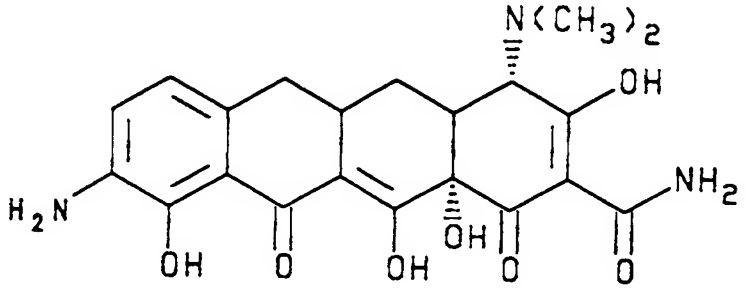
R is selected from hydrogen, methyl and ethyl;

R^1 is selected from hydrogen, methyl or ethyl;
when R does not equal R^1 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the Y substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts and metal complexes.

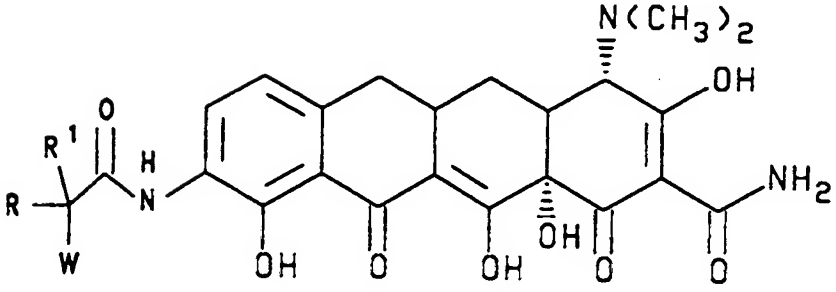
DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0013] The novel compounds of the present invention may be readily prepared in accordance with the following schemes.

Scheme I

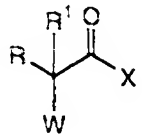


1 mineral acid salt



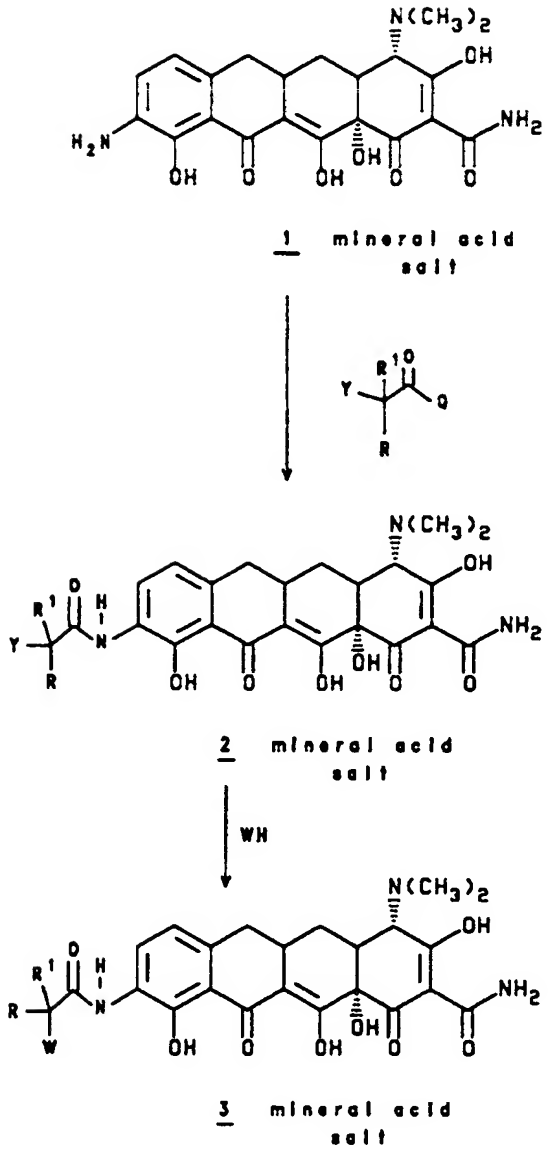
3 mineral acid salt

[0014] The 9-[(substituted glycyl)amido]-6-demethyl- 6-deoxytetracyclines, or mineral acid salts, can be made by the procedure described in scheme I. In accordance with scheme I, 9-amino-6-demethyl-6-deoxy- tetracycline or its mineral acid salt, 1, is dissolved in a mixture of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)- pyrimidone and acetonitrile. Sodium carbonate is added and the mixture is stirred for 5 minutes. An acid halide of the formula:

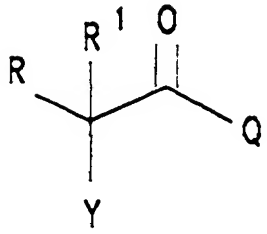


wherein R, R^1, W have been described hereinabove, and X is selected from chlorine, fluorine, bromine or iodine, is added and the reaction is stirred at room temperature for from 0.5-2 hours to give the corresponding 9-[(substituted glycyl)amido]-6-demethyl-6-deoxytetracycline, or its mineral acid salt 3.

Scheme II



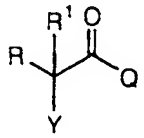
[0015] The preferred method for producing 9-[(substituted glycyl)amido]-6-demethyl-6-deoxytetracyclines or its mineral acid salt 3, is shown in scheme II. This method uses common intermediates which are easily prepared by reacting commercially available haloacyl halides of the formula:



wherein Y, R and R^1 are as defined hereinabove and Q is halogen selected from bromine, chlorine, iodine and fluorine; with 9-amino-6-demethyl-6-deoxytetracyclines, or its mineral acid salt 1, to give straight or branched 9-[(haloacyl) amido]-6-demethyl-6-deoxytetracyclines or its mineral acid salt, 2, in almost quantitative yield. The above intermediates, straight or branched 9-[(haloacyl)amido]-6-demethyl-6-deoxytetracyclines or its mineral acid salt 2, react with a wide variety of nucleophiles, especially amines, having the formula WH, wherein W is as defined hereinabove to give the new 9-[(substituted glycyl)amido]-6-demethyl-6-deoxytetracyclines or mineral acid salt 3 of the present invention.

[0016] In accordance with Scheme II, 9-amino-6-demethyl-6-deoxytetracycline or its mineral acid salt, 1, is mixed with

a) a polar-aprotic solvent such as 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidone, herein after called DMPU, hexamethylphosphoramide herein after called HMPA, dimethylformamide, dimethylacetamide, N-methylpyrrolidone, 1,2-dimethoxyethane or equivalent thereof;
b) an inert solvent such as acetonitrile, methylene chloride, tetrahydrofuran chloroform, carbon tetrachloride, 1,2-dichloroethane, tetrachloroethane, diethyl ether, t-butyl methylether, isopropyl ether or equivalent thereof;
c) a base such as sodium carbonate, sodium bicarbonate, sodium acetate, potassium carbonate, potassium bicarbonate, triethylamine, cesium carbonate, lithium carbonate or bicarbonate equivalents; and
d) a straight or branched haloacyl halide of the formula:

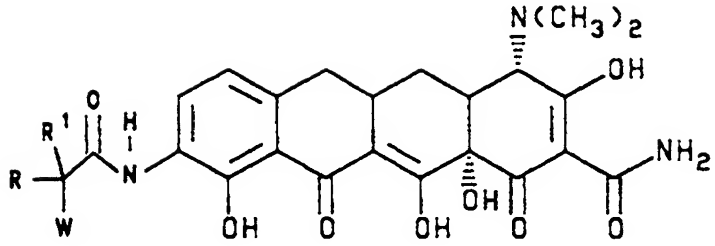


wherein Y, R, R^1 and Q are as defined hereinabove such as bromoacetyl bromide, chloroacetyl chloride or 2-bromopropionyl bromide or equivalent thereof; the halo, Y, and halide, Q, in the haloacyl halide can be the same or different halogen and are selected from bromine, chlorine, iodine and fluorine
e) for 0.5 to 5 hours at room temperature to the reflux temperature of the reaction; to form the corresponding 9-[(haloacyl)amido]-6-de-methyl-6-deoxytetracycline, 2 , or its mineral acid salt.

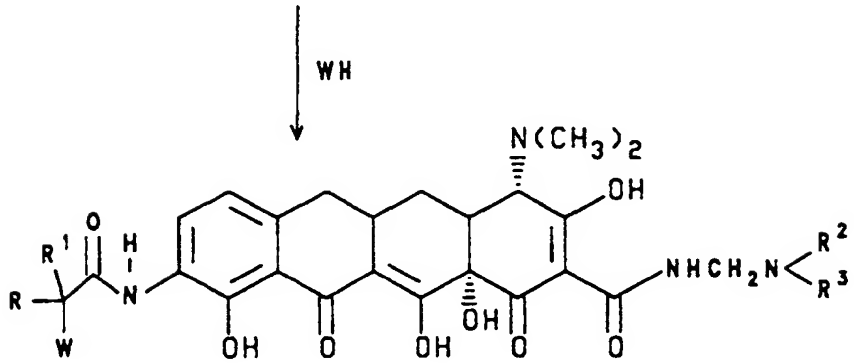
[0017] The intermediate, 9-[(haloacyl)amido]-6-demethyl-6-deoxytetracycline or mineral acid salt 2, is treated, under an inert atmosphere of helium, argon or nitrogen, with

a) a nucleophile WH such as an amine or substituted amine or equivalent for example methyl- amine, dimethylamine, ethylamine, n-butylamine, propylamine or n-hexylamine;
b) a polar-aprotic solvent such as DMPU, HMPA dimethylformamide, dimethylacetamide, N-methylpyrrolidone or 1,2-dimethoxyethane;
c) for from 0.5 - 2 hours at room temperature or under reflux temperature to produce the desired 9-[(substituted glycyl)amido]-6-demethyl-6-deoxytetracycline, 3, or its mineral acid salt.

Scheme III



3



4

[0018] In accordance with Scheme III, compounds of formula 3 are N-alkylated in the presence of formaldehyde and either a primary amine such as methylamine, ethylamine, benzylamine, methyl glycinate, (L or D)alanine, (L or D)lysine or their substituted congeners; or a secondary amine such as morpholine, pyrrolidine, piperidine or their substituted congeners to give the corresponding Mannich base adduct, 4.

[0019] The 9-[(substituted glycyl)amido]-6-demethyl-6-deoxytetracyclines may be obtained as metal complexes such as aluminum, calcium, iron, magnesium, manganese and complex salts; inorganic and organic salts and corresponding Mannich base adducts using methods known to those skilled in the art (Richard C. Larock, Comprehensive Organic Transformations, VCH Publishers, 411-415, 1989). It is well known to one skilled in the art that an appropriate salt form is chosen based on physical and chemical stability, flowability, hygroscopicity and solubility. Preferably, the 9-[(substituted glycyl)amido]-6-demethyl-6-deoxytetracyclines are obtained as inorganic salt such as hydrochloric, hydrobromic, hydroiodic, phosphoric, nitric or sulfate; or organic salt such as acetate, benzoate, citrate, cysteine or other amino acids, fumarate, glycolate, maleate, succinate, tartrate, alkylsulfonate or arylsulfonate. Depending on the stochiometry of the acids used, the salt formation occurs with the C(4)-dimethylamino group (1 equivalent of acid) or with both the C(4)-dimethylamino group and the W group (2 equivalents of acid). The salts are preferred for oral and parenteral administration.

[0020] Some of the compounds of the hereinbefore described Schemes have centers of asymmetry at the carbon bearing the W substituent. The compounds may, therefore, exist in at least two (2) stereoisomeric forms. The present

invention encompasses the racemic mixture of stereo isomers as well as all stereoisomers of the compounds whether free from other stereoisomers or admixed with stereoisomers in any proportion of enantiomers. The absolute configuration of any compound may be determined by conventional X-ray crystallography.

[0021] The stereochemistry centers on the tetracycline unit (i.e. C-4, C-4a, C-5a and C-12a) remain intact throughout the reaction sequences.

BIOLOGICAL ACTIVITY

Method for in Vitro Antibacterial Evaluation (Tables I, II and V)

[0022] The minimum inhibitory concentration (MIC), the lowest concentration of the antibiotic which inhibits growth to the test organism, is determined by the agar dilution method using Muller-Hinton II agar (Baltimore Biological Laboratories). An inoculum density of 1-5x 10^5 CFU/ml and a range of antibiotic concentrations (32-0.004 µg/ml) is used. The plates are incubated for 18 hours at 35°C in a forced air incubator. The test organisms comprise strains that are sensitive to tetracycline and genetically defined strains that are resistant to tetracycline, due to inability to bind to bacterial ribosomes (tetM) or by a tetK encoded membrane protein which confers tetracycline resistance by energy-dependent efflux of the antibiotic from the cell.

E. coli in Vitro Protein Translation System (Table III)

[0023] An in vitro, cell free, protein translation system using extracts from E. coli strain MRE600 (tetracycline sensitive) and a derivative of MRE600 containing the tetM determinant has been developed based on literature methods [J.M. Pratt, Coupled Transcription-translation in Prokaryotic Cell-free Systems, Transcription and Translation, a Practical Approach, (B.D. Hames and S.J. Higgins, eds) p. 179-209, IRL Press, Oxford-Washington, 1984].

[0024] Using the system described above, the tetracycline compounds of the present invention are tested for their ability to inhibit protein sysnthesis in vitro. Briefly, each 10 µl reaction contains S30 extract (a whole extract) made from either tetracycline sensitive cells or an isogenic tetracycline resistant (tetM) strain, low molecular weight components necessary for transcription and translation (i.e. ATP and GTP), a mix of 19 amino acids (no methionine), ^{35}S labeled methionine, DNA template (either pBR322 or pUC119), and either DMSO (control) or the novel tetracycline compound to be tested ("novel TC") dissolved in DMSO.

[0025] The reactions are incubated for 30 minutes at 37°C. Timing is initiated with the addition of the S30 extract, the last component to be added. After 30 minutes, 2.5 µl of the reaction is removed and mixed with 0.5 ml of 1N NaOH to destroy RNA and tRNA. Two ml of 25% trichloroacetic acid is added and the mixture incubated at room temperature for 15 minutes. The trichloroacetic acid precipitated material is collected on Whatman GF/C filters and washed with a solution of 10% trichloroacetic acid. The filters are dried and the retained radioactivity, representing incorporation of ^{35}S-methionine into polypeptides, is counted using standard liquid scintillation methods.

[0026] The percent inhibition (P.I.) of protein synthesis is determined to be:

$$P.I. = 100 - \left(\frac{\text{Retained radioactivity of novel TC containing sample}}{\text{Retained radioactivity of the DMSO control reaction}} \right) \times 100$$

In Vivo Antibacterial Evaluation (Table IV)

[0027] The therapeutic effects of tetracyclines are determined against an acute lethal infection with Staphylococcus aureus strain Smith (tetracycline sensitive). Female, mice, strain CD-1 (Charles River Laboratories), 20±2 grams, are challenged by an intraperitoneal injection of sufficient bacteria (suspended in hog mucin) to kill non-treated controls within 24-48 hours. Antibacterial agents, contained in 0.5 ml of 0.2% aqueous agar, are administered subcutaneously or orally 30 minutes after infection. When an oral dosing schedule is used, animals are deprived of food for 5 hours before and 2 hours after infection. Five mice are treated at each dose level. The 7 day survival ratios from 3 separate tests are pooled for calculation of median effective dose (ED_{50}).

Testing Results

[0028] The claimed compounds exhibit antibacterial activity against a spectrum of tetracycline sensitive and resistant Gram-positive and Gram-negative bacteria, especially, strains of E. coli and S. aureus containing tetM resistance de-

terminants, and E. coli containing the tetA, tetB, tetC and tetD resistance determinants. Notable is 9-[(N,N-dimethylglycyl)amido]-6-demethyl-6-deoxytetracycline, CC, as shown in Table I, which demonstrated excellent in vitro activity against tetracycline resistant strains containing the tetM resistance determinant (such as S. aureus UBMS 88-5, S. aureus UBMS 90-1 and 90-2, E. coli UBMS 89-1 and 90-4) and tetracycline resistant strains containing tetB resistance determinants (such as E. coli UBMS 88-1 and E. coli TN10C tetB). 9-[(N,N-dimethylglycyl)amido]-6-demethyl-6-deoxytetracycline, also has good activity against E. coli strains containing tetA, tetC and tetD resistance determinants. It is as effective as minocycline against susceptible strains and is superior to minocycline against a number of recently isolated bacteria from clinical sources. (Table II)

[0029] As shown in Table II, the free base, disulfate, dihydrochloride, monohydrochloride and the Mannich bases of 9-[(N,N-dimethylglycyl)amindo]-6-demethyl-6-deoxytetracycline, show comparable in vitro antibacterial activity.

[0030] Minocycline and 9-[(N,N-dimethylglycyl)-amido]-6-demethyl-6-deoxytetracycline are assayed for their ability to inhibit protein synthesis taking place on either wild type or TetM modified ribosomes using a coupled transcription and translation system. Both compounds effectively inhibit protein synthesis occurring on wild type ribosomes, at equivalent levels of activity. Minocycline is not effective in inhibiting protein synthesis occurring on tetM modified ribosomes. In contrast, 9-[(N,N-dimethylglycyl)amido]-6-demethyl-6-deoxytetracycline is effective at inhibiting protein synthesis occuring on TetM modified ribosomes, although a slightly higher concen-tration is required to achieve similar levels of inhibition relative to wild type ribosomes. (Table III)

[0031] 9-[(N,N-Dimethylglycyl)amido]-6-demethyl-6-deoxytetracycline binds reversibly to its target (the ribosome) since bacterial growth resumes when the compound is removed by washing of the organism. Therefore, the ability of 9-[(N,N-dimethylglycyl)-amido]-6-demethyl-6-deoxytetracycline to inhibit bacterial growth appears to be a direct consequence of its ability to inhibit protein synthesis at the ribosome level.

[0032] As shown in Table IV, the claimed compounds AA, BB, DD, CC, H, C, D, G and Q show very good in vivo activity when tested intraveneously against the minocycline sensitive organism, S. aureus Smith. The claimed compound CC when administered intraveneously exhibits potent activity (ED_{50} 1.6 mg/kg) against E. coli UBMS 90-4 (TetM), which is resistant to minocycline, i.e. (ED_{50} >32 mg/kg).

[0033] As shown in Table V, 9-[(N,N-dimethylglycyl)-amido)]-6-demethyl-6-deoxytetracycline shows potent in vitro antibacterial activity against a broad spectrum of recent clinical isolates, including a number from veterinary sources. It was more active than minocycline and tetracycline against the majority of the isolates tested. The claimed compound is especially active against E. faecalis, E. faecium including vancomycin resistant strains. The 9-[(dimethylglycyl)-amido]-6-demethyl-6-deoxytetracycline also exhibits potent activity against E. coli, Salmonella spp., Shigella spp., Salmonella choleraesuis, Proteus mirabilis, Proteus vulgaris, Morganella morganii, Neisseria gonorrhoeae, Bacteroides spp., Clastridium spp. and Streptococcus spp. The activity of the 9-[(N,N-dimethylglycyl)amido]-6-demethyl-6-deoxytetracycline is generally greater than minocycline and tetracycline.

[0034] As can be seen from Tables I-V, compounds of the invention can be used to prevent or control important mammalian and veterinary diseases such as diarrhea, urinary tract infections, infections of skin and skin structure, ear, nose and throat infections, wound infections, mastitis and the like.

[0035] Thus, the improved efficacy of 9-[(N,N-dimethylglycyl)amido]-6-demethyl-6-deoxytetracycline is demonstrated by the in vitro activity against isogenic strains into which the resistance determinants, such as tetM, are cloned (Table I); the inhibition of protein synthesis by TetM modified ribosomes (Table III); and the in vivo activity against experimental infections caused by strains resistant to the tetracyclines, due to the presence of resistance determinants, such as tet M (Table IV).

[0036] When the compounds are employed as antibacterials, they can be combined with one or more pharmaceutically acceptable carriers, for example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing for example, from about 20 to 50% ethanol and the like, or parenterally in the form of sterile injectable solutions or suspensions containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 25 to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

[0037] An effective amount of compound from 2.0 mg/kg of body weight to 100.0 mg/kg of body weight should be administered one to five times per day via any typical route of administration including but not limited to oral, parenteral (including subcutaneous, intravenous, intramuscular, intrasternal injection or infusion techniques), topical or rectal, in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[0038] These active compounds may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

[0039] The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred.

[0040] These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in glycerol, liquid, polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[0041] The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserve against the contaminating action of micoorganisms such as bacterial and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oil.

[0042] The invention will be more fully described in conjunction with the following specific examples which are not be construed as limiting the scope of the invention.

COMPOUND LEGEND FOR TABLES	
A	[7S-(7alpha, 10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-methyl-1-piperidineacetamide dihydrochloride
B	[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[2-(dimethylamino)-1-oxopropyl]amino]-1,4, 4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride
C	[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4, 4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(propylamino)acetyl]-amino]-2-naphthacenecarboxamide dihydrochloride
D	[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-pyrrolidineacetamide dihydrochloride
E	[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[(ethylamino)acetyl]amino]-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride
F	[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4, 4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[(methylamino)acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride
G	[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[(hexylamino)acetyl]amino]-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride
H	[4S-(4alpha,12aalpha)]-9-[[(Butylamino)-acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride
I	[7S-(7alpha, 10aalpha)]-N-9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-1-piperidineacetamide dihydrochloride (331,404)
J	[45-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4, 4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(phenylmethyl)amino]acetyl]amino]-2-naphthacenecarboxamide dihydrochloride
K	[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4, 4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(pentylamino)acetyl]amino]-2-naphthacenecarboxamide monohydrochloride
L	[4S-(4alpha, 12aalpha)]-4-(Dimethylamino)-1,4, 4a, 5, 5a, 6, 11, 12a-octahydro-3, 10, 12, 12a-tetrahydroxy-1,11-dioxo-9-[[[(2-thienylmethyl)amino]acetyl]amino]-2-naphthacenecarboxamide dihydrochloride
M	[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4, 4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(2-methylpropyl)amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride
N	[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4, 4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(2-pyridinylmethyl]amino]acetyl]amino]-2-naphthacenecarboxamide dihydrochloride
O	[4S-(4alpha,12aalpha)]-9-[[(Diethylamino)acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12.12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride

(continued)

COMPOUND LEGEND FOR TABLES	
P	[7S-(7alpha,10aalpha)]-N-9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-a-methyl-1-pyrrolidinecarboxamide
Q	[4S-(4alpha,12aalpha)]-9-[[[(Cyclopropylmethyl)amino]acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride
R	[4S-(4alpha,12aalpha)]-9-[(Bromoacetyl)amino]-4-(dimethylamino) 1,4,4a,5,5a,6,11 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride
S	[4S-(4alpha,12aalpha)]-9-[(2-Bromo-1-oxopropyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6, 11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1, 11-dioxo-2-naphthacenecarboxamide dihydrochloride
T	Tetracycline
U	Minocycline
AA	[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide disulfate
BB	[4S-(4alpha, 12aalpha)]-4-(Dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
CC	[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride
DD	[4S-(4alpha, 12aalpha)]-4-(Dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride
EE	[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-N-(1-pyrrolidinylmethyl)-2-naphthacenecarboxamide

Table I

ANTIBACTERIAL ACTIVITY OF 9-[(SUBSTITUTED GLYCYL)AMIDO]-6-DEMETHYL-6-DEOXYTETRACYCLINES

MIC (µg/ml)

Organism	Compound A	B	C	D	E	F	G	H	I	J	K
E. coli UBMS 88-1 Tet B	1	1	0.5	0.25	0.5	1	1	0.25	1	4	1
E. coli J3272 Tet sens	NT	NT	NT	NT	NT	NT	NT	0.12	NT	NT	NT
E. coli MC 4100 Tet sens.	0.25	0.25	0.12	0.12	0.25	0.5	0.12	NT	0.25	0.5	0.5
E. coli PRP1 Tet A	1	2	1	0.25	2	4	1	0.25	1	4	0.5
E. coli MC 4100 TNIOC Tet B	1	0.5	0.5	0.25	1	1	1	0.25	1	4	0.5
E. coli J3272 Tet C	1	1	0.5	0.25	1	4	1	0.12	1	4	0.5
E. coli UBMS 89-1 Tet M	0.25	0.5	0.25	0.12	0.25	0.5	0.25	0.12	0.25	2	0.25
E. coli UBMS 89-2 Tet sens.	0.5	1	0.25	0.25	0.5	1	1	0.12	0.5	4	0.25
E. coli J2175	0.5	1	0.25	0.25	0.5	0.5	1	0.25	0.5	4	0.5
E. coli BAJ9003 IMP MUT	0.12	0.25	0.06	0.06	0.12	0.5	0.12	0.06	0.12	0.5	0.25
E. coli UBMS 90-4 Tet M	0.5	0.5	0.25	0.25	0.25	0.5	0.5	0.12	0.5	4	0.5
E. coli UBMS 90-5	0.5	0.5	0.25	0.25	0.5	0.5	1	0.12	0.5	4	0.5
E. coli #311 (MP)	0.25	0.5	0.5	0.25	0.5	0.5	1	0.12	0.5	4	0.5
E. coli ATCC 25922	0.25	0.5	0.12	0.12	0.25	0.5	1	0.12	0.5	4	0.5
E. coli J3272 Tet D	0.25	0.5	0.12	0.12	0.25	0.5	0.5	0.06	0.5	4	0.5
S. marcescens FPOR 8733	8	8	4	2	4	4	8	2	8	>32	4
X. maltophilia NEMC 87210	0.5	2	4	1	8	16	1	1	0.5	16	1
Ps. aeruginosa ATCC 27853	>32	32	16	16	16	32	32	8	>32	>32	32
S. aureus NEMC 8769	no growth	0.06	0.06	0.06	0.12	0.25	0.12	0.03	0.5	1	0.12

Table I (cont'd)

ANTIBACTERIAL ACTIVITY OF 9-[(SUBSTITUTED GLYCYL)AMIDO]-6-DEMETHYL-6-DEOXYTETRACYCLINES

MIC (μg/ml)

Organism	Compound A	B	C	D	E	F	G	H	I	J	K
S. aureus UBMS 88-4	0.5	0.25	0.25	0.12	0.5	0.5	0.25	0.06	0.5	1	0.25
S. aureus UBMS 88-5 Tet M	0.5	0.5	0.5	0.12	0.5	1	0.5	0.06	0.5	2	0.5
S. aureus UBMS 88-7 Tet K	1	1	2	0.5	8	16	1	1	0.5	4	2
S. aureus UBMS 90-1 Tet M	1	0.5	0.25	0.25	0.5	0.5	1	0.12	0.5	4	0.5
S. aureus UBMS 90-3	0.5	0.06	0.06	0.12	0.12	0.5	0.25	0.03	0.25	0.5	0.25
S. aureus UBMS 90-2 Tet M	0.5	0.25	0.25	0.25	0.12	0.5	0.25	0.12	0.25	1	0.25
S. aureus IVES 2943	0.5	1	4	1	16	>32	2	1	1	4	2
S. aureus ROSE (MP)	2	4	16	2	>32	>32	4	4	4	8	8
S. aureus SMITH (MP)	0.5	0.25	0.12	0.12	0.25	0.5	0.25	0.12	0.25	0.5	0.25
S. aureus IVES 1 983	1	1	4	1	8	16	1	2	1	4	2
S. aureus ATCC 29213	0.5	0.25	0.25	0.12	0.5	0.5	0.5	0.06	0.5	1	0.5
S. hemolyticus AVHAH 88-3	2	1	0.5	0.25	1	1	2	0.5	2	4	2
Enterococcus 12201	0.5	0.25	0.25	0.12	0.25	0.5	0.25	0.12	0.25	2	0.25
E. faecalis ATCC 29212	0.25	0.25	0.12	0.12	0.25	0.5	0.12	0.12	0.25	0.25	0.25

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Table I (cont'd)

ANTIBACTERIAL ACTIVITY OF 9-[(SUBSTITUTED GLYCYL)AMIDO]-6-DEMETHYL-6-DEOXYTETRACYCLINES

MIC (μg/ml)

Organism	Compound									
	L	M	N	O	P	Q	R	S	T	U
E. coli UBMS 88-1 Tet B	32	1	>32	1	2	0.5	>32	>32	>32	16
E. coli J3272 Tet sens	NT	NT	NT	NT	NT	NT	32	4	1	1
E. coli MC 4100 Tet sens.	8	0.25	8	0.5	0.25	0.25	NT	NT	0.25	0.12
E. coli PRP1 Tet A	16	1	32	4	2	2	>32	>32	16	2
E. coli MC 4100 TN10C Tet B	32	1	32	1	2	1	>32	>32	>32	16
E. coli J3272 Tet C	32	1	>32	1	1	0.5	>32	>32	>32	1
E. coli UBMS 89-1 Tet M	8	0.5	16	0.5	0.5	0.5	8	>32	32	8
E. coli UBMS 89-2 Tet sens.	16	1	32	1	1	1	32	16	1	1
E. coli J2175	16	1	>32	1	1	1	32	16	1	1
E. coli BAJ9003 IMP MUT	4	0.25	2	0.12	0.25	0.25	1	1	0.25	0.03
E. coli UBMS 90-4 Tet M	8	0.5	16	0.5	1	0.25	32	>32	32	>32
E. coli UBMS 90-5	16	1	32	1	0.5	0.5	32	8	0.5	1
E. coli #311 (MP)	16	1	32	1	1	1	16	8	1	0.25
E. coli ATCC 25922	8	0.5	32	0.5	1	0.5	16	8	0.5	0.25
E. coli J3272 Tet D	16	0.25	32	0.5	0.5	0.25	>32	>32	>32	8
S. marcescens FPOR 8733	>32	8	>32	8	16	8	>32	>32	>32	4
X. maltophilia NEMC 87210	>32	2	>32	1	4	4	16	16	8	0.12
Ps. aeruginosa ATCC 27853	>32	32	>32	32	>32	16	>32	>32	8	8
S. aureus NEMC 8769	8	8	8	1	0.5	0.5	0.25	0.25	0.06	<0.015

Table I (cont'd)

ANTIBACTERIAL ACTIVITY OF 9-[(SUBSTITUTED GLYCYL)AMIDO]-6-DEMETHYL-6-DEOXYTETRACYCLINES

MIC (μg/ml)

Organism	Compound									
	L	M	N	O	P	Q	R	S	T	U
S. aureus UBMS 88-4	8	0.5	8	0.5	0.5	0.5	0.5	2	0.12	0.03
S. aureus UBMS 88-5 Tet M	8	0.5	8	0.5	0.5	0.5	2	32	>32	4
S. aureus UBMS 88-7 Tet K	16	2	>32	0.5	1	8	8	16	>32	0.06
S. aureus UBMS 90-1 Tet M	8	0.5	8	0.5	0.5	0.5	1	32	>32	8
S. aureus UBMS 90-3	4	0.25	4	0.25	0.25	0.5	1	2	0.12	≤0.015
S. aureus UBMS 90-2 Tet M	8	0.5	8	0.5	0.5	0.5	2	16	32	2
S. aureus IVES 2943	16	4	>32	1	2	8	16	32	>32	2
S. aureus ROSE (MP)	32	8	>32	2	8	16	16	>32	>32	0.25
S. aureus SMITH (MP)	4	0.5	4	0.25	0.5	0.5	1	1	0.12	0.03
S. aureus IVES 1983	16	2	>32	0.5	1	4	16	32	>32	4
S. aureus ATCC 29213	8	0.25	8	0.5	0.5	0.5	1	2	≤0.015	≤0.015
S. hemolyticus AVHAH 88-3	8	2	>32	2	4	4	8	8	0.5	0.06
Enterococcus 12201	8	0.5	8	0.25	0.25	0.5	4	32	32	8
E. faecalis ATCC 29212	4	0.25	4	0.25	0.25	0.25	2	16	16	2

Table 11

ANTIBACTERIAL ACTIVITY OF 9-[(SUBSTITUTED GLYCYL)AMIDO]-6-DEMETHYL-6-DEOXYTETRACYCLINES
MIC (μg/ml)

Organism	Compound						
	AA	BB	CC	DD	EE	T	U
E. coli UBMS 88-1 Tet B	0.25	0.25	0.25	0.25	0.5	>32	16
E. coli J3272 Tet sens	0.25	0.12	0.12	NT	NT	1	1
E. coli MC 4100 Tet sens.	NT	NT	NT	0.06	0.12	0.25	0.12
E. coli PRP1 Tet A	2	0.5	0.5	1	2	16	2
E. coli MC 4100 TNIOC Tet B	0.25	0.25	0.25	0.25	0.5	>32	16
E. coli J3272 Tet C	1	0.25	0.25	1	1	>32	1
E. coli UBMS 89-1 Tet M	0.25	0.12	0.12	0.5	0.25	32	8
E. coli UBMS 89-2 Tet sens.	0.25	0.25	0.25	0.25	0.5	1	1
E. coli J2175	0.25	0.25	0.25	0.25	0.5	1	1
E. coli BAJ9003 IMP MUT	0.06	no growth	no growth	0.06	0.12	0.25	0.03
E. coli UBMS 90-4 Tet M	0.25	0.12	0.12	0.12	0.25	32	>32
E. coli UBMS 90-5	0.25	0.12	0.12	0.25	0.25	0.5	1
E. coli #311 (MP)	0.50	0.12	0.12	0.25	0.5	1	0.25
E. coli ATCC 25922	0.25	0.12	0.12	0.25	0.25	0.5	0.25
E. coli J3272 Tet D	0.12	0.06	0.03	0.25	0.25	>32	8
S. marcescens FPOR 8733	4	2	2	4	4	>32	4
X. maltophilia NEMC 87210	2	1	1	2	2	8	0.12
Ps. aeruginosa ATCC 27853	16	8	4	8	16	8	8
S. aureus NEMC 8769	0.03	<0.015	<0.015	0.03	0.25	0.06	<0.015

Table 11 (cont'd)

ANTIBACTERIAL ACTIVITY OF 9-[(SUBSTITUTED GLYCYL)AMIDO]-6-DEMETHYL-6-DEOXYTETRACYCLINES

MIC (μg/ml)

Organism	Compound						
	AA	BB	CC	DD	EE	T	U
S. aureus UBMS 88-4	0.12	0.06	0.03	0.12	0.25	0.12	0.03
S. aureus UBMS 88-5 Tet M	0.12	0.12	0.03	0.12	0.25	>32	4
S. aureus UBMS 88-7 Tet K	1	0.5	0.5	1	1	>32	0.06
S. aureus UBMS 90-1 Tet M	0.25	0.12	0.06	0.12	0.25	>32	8
S. aureus UBMS 90-3	0.06	0.06	0.03	0.06	0.12	0.12	≤0.015
S. aureus UBMS 90-2 Tet M	0.12	0.12	0.06	0.12	0.25	32	2
S. aureus IVES 2943	1	0.5	0.5	1	2	>32	2
S. aureus ROSE (MP)	4	2	1	4	8	>32	0.25
S. aureus SMITH (MP)	0.12	0.06	0.03	0.12	0.25	0.12	0.03
S. aureus IVES 1983	2	0.5	0.5	1	2	>32	4
S. aureus ATCC 29213	≤0.015	0.3	≤0.015	0.12	0.25	≤0.015	≤0.015
S. hemolyticus AVHAH 88-3	0.5	0.12	0.12	0.25	0.5	0.5	0.06
Enterococcus 12201	0.12	0.06	0.03	0.12	0.25	32	8
E. faecalis ATCC 29212	0.12	0.06	0.03	0.06	0.12	16	2

NT = not tested

Table III

In Vitro Transcription and Translation Sensitivity to 9-(Glycylamido)-6-deoxy-6- demethyltetracycline Derivatives			
Compound		% Inhibition	
	Conc.	Wild Type S30	Tet M S30
CC	1.0 mg/ml	99	99
	0.25 mg/ml	98	94
	0.06 mg/ml	91	82
H	1.0 mg/ml	99	98
	0.25 mg/ml	91	95
	0.06 mg/ml	86	72
U	1.0 mg/ml	98	68
	0.25 mg/ml	89	43
	0.06 mg/ml	78	0

Table IV

Effects of Glycylcycline Derivatives on Acute Lethal Infections in Mice (ED_{50} mg/kg)

Organism	Route of Antibiotic Administration	AA	BB	DD	CC	H	C	D	G	Q	U
S. aureus Smith (Sens)	Oral	>16	8-16	12	>8	>16	>16	>16	>16	>16	0.74
	Intraveneous	0.5-1	0.5-1	0.67	0.46	0.5-1	1-2	1-2	>4	NT	0.37
Escherichia coli UBMS 90-4 (Tet M)	Intraveneous	NT	NT	NT	1.6	NT	NT	NT	NT	NT	>32

Table V

In Vitro Activity of CC and Comparative Antibiotics vs Recent Clinical and Veterinary Isolates

Organism	[# Isolates]	MIC (μg/ml) Range CC	U	T
Staphylococcus aureus, (methicillin-resistant)	[15]	0.12-4	0.06-4	0.25->64
Staphylococcus aureus, (methicillin-susceptible)	[15]	0.06-0.25	0.03-0.12	0.12-1
Staphylococcus Coagulase-negative, (methicillin-resistant)	[16]	0.06-16	0.03-1	0.12->64
Staphylococcus Coagulase-negative, (methicillin-susceptible)	[14]	0.06-4	0.015-0.25	0.12->64
Enterococcus faecalis	[10]	0.03-0.25	0.03-16	0.12-64
Enterococcus faecium	[10]	0.06-0.5	0.03-16	0.12-64
Enterococcus spp. (Vancomycin-resistant)	[8]	0.03-0.12	0.03-16	0.12->64
Streptococcus pyogenes	[10]	0.06-0.12	0.03-2	0.12-16
Streptococcus agalactiae	[10]	0.12-0.25	0.12-16	0.25-64

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Table V (cont'd)

In Vitro Activity of CC and Comparative Antibiotics vs Recent Clinical and Veterinary Isolates

Organism	[# Isolates]	MIC (μg/ml) Range CC	U	T
Streptococcus pneumoniae	[10]	0.03-0.5	0.06-0.5	0.12-2
Listeria monocytogenes	[8]	0.06-0.12	0.015-0.03	0.12-0.5
Escherichia coli	[30]	0.25-4	0.25-32	0.5->64
Escherichia coli (Veterinary)	[15]	0.25-4	1-16	2->64
Shigella spp.	[14]	0.12-0.5	0.25-8	0.25->64
Klebsiella pneumoniae	[10]	0.25-4	0.5-8	0.5->64
Klebsiella oxytoca	[10]	0.25-1	0.5-4	0.5-1
Citrobacter freundii	[10]	0.5-8	0.03-32	0.5-16
Citrobacter diversus	[10]	0.25-1	0.25-4	0.5-4
Salmonella spp.	[11]	0.25-0.5	0.5-16	0.5->64
Salmonella choleraesuis (Veterinary)	[15]	0.5-8	2->64	1->64

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Table V (cont'd)

In Vitro Activity of CC and Comparative Antibiotics vs Recent Clinical and Veterinary Isolates

Organism	[# Isolates]	MIC (μg/ml) Range CC	U	T
Serratia marcescens	[10]	2-8	1-8	8->64
Enterobacter cloacae	[10]	0.5-1	0.25-4	0.5-2
Enterobacter aerogenes	[10]	0.25-1	0.5-1	0.5-1
Providencia spp.	[13]	1-8	4->64	1->64
Proteus mirabilis	[26]	0.12-2	1-32	0.5-64
Proteus vulgaris	[18]	0.06-1	0.5-16	0.25-64
Morganella morganii	[16]	0.5-1	0.25-32	0.25->64
Pseudomonas aeruginosa	[10]	2-16	1-16	2-32
Xanthamonas maltophilia	[10]	1-8	0.12-1	8-16
Moraxella catarrhalis	[18]	0.06-0.12	0.03-0.12	0.06-0.5
Neisseria gonorrhoeae	[14]	0.5-1	0.5-64	1->64
Haemophilus influenzae	[15]	1-2	0.5-2	1-32

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Table V (cont'd)

In Vitro Activity of CC and Comparative Antibiotics vs Recent Clinical and Veterinary Isolates

Organism	[# Isolates]	MIC (μg/ml) Range CC	U	T
Pasturella multocida (Veterinary)	[17]	0.03-0.25	0.015-4	0.06-16
Bordetella bronchiseptica (Veterinary)	[10]	0.06-0.12	0.06-0.12	0.12-0.25
Bacteroides fragilis	[11]	0.25-1	<0.008-16	0.25->64
Bacteroides fragilis group	[10]	0.12-2	<0.008-4	0.25-32
Bacteroides spp.	[9]	0.12-0.5	0.03-16	0.25->64
Clostridium difficile	[12]	0.06-0.12	0.015-16	0.12-32
Clostridium perfringens	[16]	0.03-2	<0.008-16	0.015-16
Clostridium spp.	[9]	0.03-0.12	<0.008-16	0.015-64
Anaerobic Gram(+)Cocci	[15]	0.015-0.12	0.05-8	4->64

Example 1

[4S-(4alpha, 12aalpha)1-9-[(Bromoacetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride **(Formula III, R and R^1=H, Y is Br, HCl salt)** and

[4S-(4alpha,12aalpha)1-9-[(Chloroacetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride **(Formula III, R and R^1=H, Y is Cl, HCl salt)**

[0043] To a room temperature solution of 1.58 g of 9-amino-6-demethyl-6-deoxytetracycline monosulfate, 20 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone, hereinafter called DMPU, and 4 ml of acetonitrile is added 0.50 g of sodium carbonate. The mixture is stirred for 5 minutes followed by the addition of 0.942 g of bromoacetyl chloride. The reaction is stirred for 1 hour, filtered, and the filtrate added dropwise to a mixture of 50 ml of isopropanol and 500 ml of diethyl ether. The resulting solid is collected, washed first with the mixed solvent (isopropanol and diethyl ether) followed by diethyl ether, and dried to give 1.62 g of a mixture of the desired products. MS(FAB): m/z 550 (M+H) and 506 (M+H).

Example 2

[4S-(4alpha,12aalpha)]-9-[(Bromoacetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrobromide **(Formula III, R and R^1=H, Y is Br, HBr salt)**

[0044] The title compound is prepared by the procedure of Example 1 using 1.2 g of bromoacetyl bromide to give 1.49 g of the pure desired product.
1H NMR(D6-DMSO) : d 12.1(s,1H), 9.9 (bs,1H), 9.8 (s,1H), 9.55(s,1H), 9.05(s,1H), 8.05(d,1H), 6.8(d,1H), 4.3(s,1H), 4.2(s,2H), 2.75(s,6H).

Example 3

[4S-(4alpha, 12aalpha)1-9-[(Bromoacetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monosulfate **(Formula III, R and R^1=H, Y is Br, monosulfate salt)**

[0045] To a room temperature solution of 1.05 g of 9-amino-6-demethyl-6-deoxytetracycline monosulfate, 10 ml of DMPU and 2 ml of acetonitrile is added 0.605 g of bromoacetyl bromide. The mixture is stirred for 30 minutes, then poured slowly into a mixture of 5 ml methyl alcohol, 50 ml isopropyl alcohol and 500 ml of diethyl ether. The resulting yellow solid is collected, washed several times with diethyl ether and dried to give 1.27 g of the desired product.
1H NMR(D6-DMSO): d 12.1(s,1H), 9.9(bs,1H), 9.8(s,1H), 9.55(s,1H), 9.05(s,1H), 8.05(d,1H), 6.8(d,1H), 4.3(s,1H), 4.2 (s,2H), 2.75(s,6H) .

Example 4

[4S-(4alpha, 12aalpha)1-9-[(Chloroacetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride **(Formula III, R and R^1=H, Y is Cl, HCl salt)**

[0046] To a room temperature solution of 0.0465 g of 9-amino-6-demethyl-6-deoxytetracycline hydrochloride, 1.5 ml of DMPU and 0.5 ml of acetonitrile is added 0.023 g of chloroacetyl chloride. The mixture is stirred for 30 minutes, then poured into a mixture of 0.5 ml of methyl alcohol, 2 ml of isopropyl alcohol and 20 ml of diethyl ether. The resulting solid is collected, washed with diethyl ether and dried to give 0.042 g of the desired product.
MS(FAB): m/z 506 (M+H).
1H NMR(D6-DMSO) : d 12.1 (s,1H), 10.4(bs,1H), 9.75(s,1H), 9.55(s,1H), 9.05(s,1H), 8.05(d,1H), 6.8(d,1H), 4.4(s,2H), 4.3(s,1H), 2.8(s,6H).

Example 5

[4S-(4alpha, 12aalpha)]-9-[(2-Bromo-1-oxopropyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10-12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrobromide **(Formula III, R = CH_3, R^1 = H, Y is Cl, HBr salt)**

[0047] The title compound is prepared by the procedure of Example 1, using 2.11 g of 9-amino-4-(dimethylamino)-6-demethyl-6-deoxytetracycline monosulfate, 0.7 g of sodium carbonate, 20 ml of DMPU, 8 ml of acetonitrile and 1.73 g of 2-bromopropionyl bromide. The reaction is stirred for 1 hour to give 1.75 g of the desired product. This reaction works equally well without sodium carbonate. MS(FAB) : m/z 564 (M+H).

Example 6

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[(hexylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride **(Formula I, R and R^1 = H, W = n-hexylamino di HCl salt)**

[0048] A mixture of 0.23 g of product from Example 2, 0.80 g of n-hexylamine and 5 ml of DMPU, under argon, is stirred at room temperature for 2 hours. The reaction is concentrated in vacuo and the residue diluted with a small volume of methanol. The diluted reaction solution is added dropwise to a mixture of 10 ml of isopropyl alcohol and 100 ml of diethyl ether. 2M hydrochloric acid in diethyl ether is added until a yellow solid is observed. The resulting solid is collected, washed with diethyl ether and dried to give 0.14 g of the desired product.

[0049] Substantially following the methods described in detail herein above in Example 6, the compounds of this invention listed below in Examples 7 - 22 are prepared.

Example 7	Formula I R and R^1 = H	W = methylamino, di HCl salt
Example 8	Formula I R and R^1 = H	W = ethylamino, di HCl salt
Example 9	Formula I R and R^1 = H	W = pyrrolidin-1-yl, di HCl salt
Example 10	Formula I R and R^1 = H	W = 4-methylpiperidin-1-yl, di HCl salt
Example 11	Formula I R and R^1 = H	W = propylamino, di HCl salt
Example 12	Formula I R and R^1 = H	W = n-butylamino, di HCl salt
Example 13	Formula I R =CH_3, R^1 = H	W = dimethylamino, di HCl salt
Example 14	Formula I R and R^1 = H	W = pentylamino, di HCl salt
Example 15	Formula I R and R^1 = H	W = piperidino, di HCl salt
Example 16	Formula I R and R^1 = H	W = benzylamino, di HCl salt
Example 17	Formula I R and R^1 = H	W = thien-2-ylmethylamino, di HCl salt
Example 18	Formula I R and R^1 = H	W = isobutylamino, di HCl salt
Example 19	Formula I R and R^1 = H	W = pyridin-2-yl-methylamino, di HCl salt
Example 20	Formula I R and R^1 = H	W = diethylamino, di HCl salt
Example 21	Formula I R =CH_3, R^1 = H	W = pyrrolidin-1-yl,
Example 22	Formula I R and R^1 = H	W = cyclopropylmethylamino, di HCl salt

Example #	Name	Starting Material Prod. of Exp.	Reactant	Rx Time	MS(FAB): m/z
7	[4S-(4alpha,12aalpha)]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[(methylamino)acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	2	Methylamine (40% in water)	2.5 hrs.	501(M+H)
8	[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[(ethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	2	Ethylamine (70% in water)	0.5 hr.	515(M+H)
9	[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,-7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-pyrrolidineacetamide dihydrochloride	2	Pyrrolidine	0.5 hr.	541(M+H)
10	[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,-10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-methyl-1-piperidineacetamide dihydrochloride	2	4-Methylpiperidine	1.5 hr.	569(M+H)
11	[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(propylamino)-acetyl]amino]-2-naphthacenecarboxamide dihydrochloride	2	Propylamine	1 hr.	529(M+H)

Example #	Name	Starting Material Prod. of Exp.	Reactant	Rx Time	MS(FAB): m/z
12	[4S-(4alpha,12aalpha)]-9-[[(Butylamino)acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	1 or 3	n-Butylamine	2 hr.	543(M+H)
13	[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[2-(dimethylamino)-1-oxopropyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	5	Dimethylamine	2 hr.	529(M+H)
14	[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(pentylamino)acetyl]amino]-2-naphthacenecarboxamide monohydrochloride	1	Amylamine	2 hr.	557(M+H)
15	[7S-(7alpha,10aalpha)]-N-9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,-10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-1-piperidineacetamide dihydrochloride	3	Piperidine	1 hr.	555(M+H)

Example #	Name	Starting Material Prod. of Exp.	Reactant	Rx Time	MS(FAB).: m/z
16	[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(phenylmethyl)amino]acetyl]amino]-2-naphthacenecarboxamide dihydrochloride	3	Benzylamine	1 hr.	577(M+H)
17	[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(2-thienylmethyl)amino]acetyl]amino]-2-naphthacenecarboxamide dihydrochloride	1	2-Thiophenemethylamine	1 1/2 hr.	583(M+H)
18	[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(2-methylpropyl)amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	3	Isobutylamine	1 1/2 hr.	543(M+H)
19	[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(2-pyridinylmethyl]amino]acetyl]amino]-2-naphthacenecarboxamide dihydrochloride	3	2-(Aminomethyl) pyridine	1 1/2 hr.	578(M+H).

Example #	Name	Starting Material of Exp. Prod.	Reactant	Rx Time	MS(FAB): m/z
20	[4S-(4alpha,12aalpha)]-9-[[(Diethylamino)acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	3	Diethylamine	1 1/2 hr.	543(M+H)
21	[7S-(7alpha,10aalpha)]-N-9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-alpha-methyl-1-pyrrolidinecarboxamide	5	Pyrrolidine	1 hr.	555(M+H)
22	[4S-(4alpha,12aalpha)]-9-[[[(Cyclopropylmethyl)amino]acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	3	(Aminomethyl) cyclopropane	1 hr.	541(M+H)

Example 23

[4S-(4alpha, 12aalpha)1-4-(Dimethylamino)-9-[[(dimethylamino)acetyllaminol-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate, dihydrochloride, monohydrochloride or free base **(Formula I, R and R^1 = H, W = dimethylamino)**

[0050] A mixture of 0.264g of 9-amino-6-demethyl-6-deoxytetracycline, obtained by literature procedures, 5 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidinone, 2 ml of acetonitrile and 0.3 g of sodium carbonate is stirred at room temperature for 5 minutes.

To this mixture is added 0.094 g of N,N-dimethylglycyl chloride hydrochloride. The reaction is allowed to stir for 30 minutes at room temperature and then filtered. The filtrate is added dropwise to approximately 300 ml of diethyl ether containing a few drop of either concentrated sulfuric or hydrochloric acid. The resulting precipitate is collected, washed with diethyl ether and dried to yield 0.12 g of the desired product.

[0051] The hydrochloride salt is converted, by treatment with ammonium hydroxide, to the free base. MS(FAB): m/z 515 (M+H).

[0052] Alternatively, the title compound is prepared by the procedure of Example 3, using 0.2 g of product from Example 1, 2, 3 or 4, 1.25 g of dimethylamine (40% in water) and 5 ml of DMPU to give 0.14 g of the desired product.

Example 24

General Procedure for the Preparation of Mannich Bases.

[0053] A mixture of 0.5 mm of product from Example 20 (free base), 3 ml of t-butyl alcohol, 0.55 mm of 37% formaldehyde, and 0.55 mm of pyrrolidine, morpholine or piperidine is stirred at room temperature for 30 minutes followed by heating at 100°C for 15 minutes. The reaction mixture is cooled to room temperature and triturated with diethyl ether and hexane. The solid is collected, washed with diethyl ether and hexane, and dried to give the desired product.

In this manner the following compound is made: [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3, 10,12,12a-tetrahydroxy-1,11-dioxo-N-(1-pyrrolidinylmethyl)-2-naphthacenecarboxamide **(Formula II, R and R^1 = H, W = NMe_2 and NR^2R^3 = pyrrolidino)**

[0054] Substantially following the method described in Example 6, the compounds of this invention listed below in Examples 25-48 are prepared using the product from Example 3 or 4.

Example 25

[4S-(4alpha,12aalpha)1-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[(methoxyamino)acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R and R^1 = H, W = methoxyamino)**

Example 26

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(phenylmethoxy)aminolacetyl]amino]-2-naphthacenecarboxamide **(Formula I, R and R^1 = H, W = benzyloxyamino)**

Example 27

[7S-(7alpha, 10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-ethyl-1H-pyrazole-1-acetamide **(Formula I, R and R^1 = H, W = 4-ethyl-IH-pyrazol-1-yl)**

Example 28

[4S-(4alpha, 12aalpha)]-9-[[(Cyclobutylmethylamino)-acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide **(Formula I, R and R^1 = H, W = cyclobutylmethyl-amino)**

Example 29

[4S-(4alpha,12aalpha)]-9-[[(2-Butenylamino)acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R and R^1 = H, W =2-butenylamino)**

Example 30

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[(hydroxyamino)acetyl]amino]-1,11-dioxo-2-naphthacene-carboxamide. **(Formula I, R and R^1 = H, W = hydroxyamino)**

Example 31

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[methyl-(phenylmethyl)amino]acetyl]aminol-2-naphthacenecarboxamide **(Formula I, R and R^1 = H, W = N-methylbenzylamino)**

Example 32

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12dioxo-2-naphthacenyl]-5-methyl-2,5-diazabicyclo[2.2.1.]heptane-2-acetamide **(Formula I, R and R^1 = H, W = 5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl)**

Example 33

[7S-(7alpha, 10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-3-methyl-4-morpholineacetamide **(Formula I, R and R^1 = H, W = 3-methyl-4-morpholinyl)**

Example 34

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-2-azabicyclo[2.2.1]heptane-2-acetamide **(Formula I, R and R^1 = H, W = 2-azabicyclo[2.2.1]hept-2-yl).**

Example 35

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-6-methyl-2-azabicyclo[2.2.2]octane-2-acetamide **(Formula I, R and R^1 = H, W = 6-methyl-2-azabicyclo[2.2.2]octan-2-yl).**

Example 36

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-methyl-1-piperazinecarboxamide **(Formula I, R and R^1 = H, W = 4-methylpiperazin-1-yl).**

Example 37

[7S-(7alpha, 10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-hydroxy-1-piperazineacetamide **(Formula I, R and R^1 = H, W = 4-hydroxypiperazin-1-yl))**

Example 38

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-3-methyl-1-piperazinecarboxamide **(Formula I, R and R^1 = H, W = 3-methylpiperazin-1-yl)**

Example 39

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-3-cyclopropyltetrahydro-4H-thiazine-4-acetamide **(Formula I, R and R^1 = H, W = 3-cyclopropyl-tetrahydro-4H-thiazin-4-yl))**

Example 40

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-3-ethyl-1H-pyrrole-1-acetamide **(Formula I, R and R^1 = H, W = 3-ethyl-1H-pyrrol-1-yl))**

Example 41

[4S-(4alpha,12aalpha)1-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[(1H-imidazol-2-ylmethylamino)acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R and R^1 = H, W = 1H-imidazol-2-ylmethylamino)**

Example 42

[7S-(7alpha,10aalpha)]-N-[2-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-2-oxoethyl]alanine **(Formula I, R and R^1 = H, W = 1-carboxyethylamino)**

Example 43

[7S-(7alpha,10aalpha)]-N-[2-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-2-oxoethyl]carbamic acid 1,1-dimethylethyl ester **(Formula I, R and R^1 = H, W = 1,1-dimethylethoxycarbonylamino)**

Example 44

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(2-methylcyclopropyl)oxy]amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R and R^1 = H, W = (2-methylcyclopropyl)oxyamino)**

Example 45

[4S-(4alpha,12aalpha)]-9-[[[(Bicyclo[2.2.2]oct-2-yloxy)aminolacetyllaminol-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R and R^1 = H, W = bicyclo [2.2.2]oct-2-yloxyamino)**

Example 46

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9- [[[(3-methyl-2-butenyl) amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R and R^1 = H, W = 3-methyl-2-butenylamino)**

Example 47

[4S-(4alpha,12aalpha)1-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-f [[[4-[(2-methyl-1-oxopropyl)amino]phenyl]amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R and R^1 = H, W = 4-[(2-methyl-1-oxopropyl)amino]phenylamino)**

Example 48

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-3-ethyl-1-pyrrolidineacetamide **(Formula I, R and R^1 = H, W = 3-ethylpyrrolidin-1-yl)**

[0055] Substantially following the method described in Example 6, the compounds of this invention listed below in Examples 49-55 are prepared using the product from Example 5.

Example 49

[4S-(4alpha,12aalpha)1-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[2-[[(1-methyl-1H-imidazol-2-yl)methyl]amino]-1-oxopropyl]amino]-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R = CH_3, R^1 = H, W = 1-methyl-1H-imidazol-2-yl)methylamino)**

Example 50

[4S-(4alpha,12aalpha)]-9-[[2-(Dicyclopropylamino)-1-oxopropyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,-11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R = CH_3, R^1 = H, W = dicyclopropylamino)**

Example 51

[7S-(7alpha,10aalpha)1-N-[9-(Aminocarbonyl)-7-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a -tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-methoxy-α-methyl-1-piperazine-carboxamide **(Formula I, R = CH_3, R^1 = H, W = 4-methoxypiperazin-1-yl)**

Example 52

[7S-(7alpha,10aalpha)1-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-tetrahydro-α,2-dimethyl-4H-1,4-thiazine-4-acetamide **(Formula I, R = CH_3, R^1= H , W = tetrahydro-2-methyl-4H-1,4-thiazin-4-yl)**

Example 53

[7S-(7alpha,10aalpha)]-[2-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]aminol-2-oxo-1-methylethyl]carbamic acid 2-propenyl ester **(Formula I, R = CH_3, R^1 = H, W = 2-propenyloxycarbonylamino)**

Example 54

[7S-(7alpha,10aalpha)l-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-(aminomethyl)-a -methyl-1-piperidineacetamide **(Formula I, R = CH_3, R^1 = H, W = 4-aminomethylpiperazin-1-yl)**

Example 55

[4S-(4alpha, 12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[2-[[3-(methylsulfonyl)phenvllaminol-1-oxopropyllaminol-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R = CH_3, R^1 = H, W = 3-(methylsulfonyl)phenylamino)**

[0056] Substantially following the method, described in detail herein above in Example 5, the compound of invention Example 56 is prepared.

Example 56

[4S-(4alpha,12aalpha)1-9-r(2-Bromo-2-methyl-1-oxopropyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide **(Formula III, R and R^1 = CH_3, Y = Br)**

Example 57

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[2-methyl-2-(methylamino)-1-oxopropyl]amino]-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R and R^1 = Me, W = methylamino)**

[0057] The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example

56 and methylamine.

Example 58

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[2-(dimethylamino)-2-methyl-1-oxopropyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R and R^1 = Me, W = dimethylamino)**

[0058] The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 56 and dimethylamine.

[0059] Substantially following the method, described in detail herein above in Example 5, the compound of invention Example 59 is prepared.

Example 59

[4S-(4alpha,12aalpha)]-9-[(2-Bromo-1-oxobutyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide **(Formula III, R = Et, R^1 = H, Y = Br)**

Example 60

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[2-[[(3-methylcyclobutyl)oxy]amino]-1-oxobutyl]amino]-1,11-dioxo-2-naphthacenecarboxamide hydrobromide **(Formula I, R = H, R^1 = Et, W = 3-methylcyclobutyloxyamino)**

[0060] The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 59 and methylcyclobutyloxyamine.

Example 61

[4S-(4alpha,12aalpha)]-9-[[2-[(1,1-dimethylethyl)methylamino]-1-oxobutyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R = Et, R^1 = H, W = N-methyl-t-butylamino).**

[0061] The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 59 and N-methyl-t-butylamine.

Example 62

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-α-ethyl-4-methyl-2-isoxazolidineacetamide **(Formula I, R = Et, R^1 = H, W = 4-methyl-isoxazolidin-2-yl)**

[0062] The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 59 and 4-methyl-2-isoxazolidine.

Example 63

[7S-(7alpha,10aalpha)1-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-α-ethyl-3-methyl-4H-1,2,4-triazole-4-acetamide **(Formula I, R = Et, R^1 = H, W = 3-methyl-4H-1,2,4-triazol-4-yl)**

[0063] The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 59 and 3-methyl-1,2,4-triazole.

[0064] Substantially following the method, described in detail herein above in Example 5, the compound of invention Example 64 is prepared.

Example 64

[4S-(4alpha, 12aalpha)]-9-[(2-Bromo-1-oxopentyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide **(Formula III R = Pr, R^1 = H, Y = Br)**

Example 65

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[2-(dimethylamino)-3,3-dimethyl-1-oxobutyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R = ^{t}Bu, R^1 = H, W = dimethylamino)**

[0065] The titled compound is prepared by the procedure of Example 6.

[0066] Substantially following the method described in detail herein above in Example 5, the compound of invention Example 66 is prepared.

Example 66

[4S-(4alpha, 12aalpha)]-9-[(2-Bromo-2-methyl-1-oxobutyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide **(Formula III, R = Et, R^1 = Me, Y = Br)**

Example 67

[4S-(4alpha, 12aalpha)]-4-(Dimethylamino)-9-[[2-(ethylamino)-2-methyl-1-oxobutyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R = Et, R^1 = Me, W = ethylamino)**

[0067] The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 66 and ethylamine.

[0068] Substantially following the method, described in detail herein above in Example 5, the compound of invention Example 68 is prepared.

Example 68

[4S-(4alpha,12aalpha)]-9-[(2-Bromo-3-hydroxy-1-oxopropyl)-amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide **(Formula III, R = CH_2OH, R^1 = H, Y = Br)**

Example 69

[4S-(4alpha,12aalpha)1-4-(Dimethylamino)-9-[[2-(dimethylamino) -3-hydroxy-1-oxopropyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R = CH_2OH, R^1 - H, W = dimethylamino)**

[0069] The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 68 and dimethylamine.

Example 70

[7S-(7alpha,10aalpha)1-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-α-(hydroxymethyl)-4-methyl-1H-imidazole-1-acetamide **(Formula I, R = CH_2OH, R^1 = H, W = 4-methyl-1H-imidazol-1-yl)**

[0070] The titled compound is prepared by the procedure *of* Example 6. The reactants are the product from Example 68 and 4-methylimidazole.

[0071] Substantially following the method, described in detail herein above in Example 5, the compound of invention Example 71 is prepared.

Example 71

[4S-(4alpha,12aalpha)]-9-[(2-Bromo-3-mercapto-1-oxopropyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide **(Formula III, R = mercaptomethyl, R^1 = H, Y = Br)**

Example 72

[4S-(4alpha,12aalpha)]-9-[[2-(Diethylamino)-3-mercapto-1-oxopropyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R = mercaptomethyl, R^1 = H, W = dimethylamino)**

[0072] The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 71 and diethylamine.

Example 73

[7S-(7alpha, 10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-α-(mercaptomethyl)-1-piperazineacetamide **(Formula I, R = mercaptomethyl, R^1 = H, W = piperazin-1-yl)**

[0073] Substantially following the method, described in detail herein above in Example 5, the compound of invention Example 74 is prepared.

Example 74

[7S-(7alpha,10aalpha)]-4-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-3-bromo-4-oxobutanoic acid hydrobromide **(Formula III, R = carboxymethyl, R^1 = H, Y = Br,)**

Example 75

[7S-(7alpha, 10aalpha]-4-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-3-(hexylamino)-4-oxobutanoic acid **(Formula I, R = carboxymethyl, R^1 = H, W = hexylamino)**

[0074] The titled compound is prepared by the procedure by Example 6. The reactants are the product from Example 74 and n-hexylamine.

Example 76

[0075] [7S-(7alpha,10aalpha)]-4-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-3-[ethyl(phenylmethyl)amino]-4-oxobutanoic acid **(Formula I, R = carboxymethyl, R^1 = H, W = N-ethylbenzylamino)**

[0076] The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 74 and N-ethylbenzylamine.

[0077] Substantially following the method, described in detail herein above in Example 5, the compound of invention Example 77 is prepared.

Example 77

[7S-(7alpha,10aalpha)1-5-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-4-bromo-5-oxopentanoic acid hydrobromide **(Formula III, R = 2-carboxyethyl, R^1 = H, Y = Br,)**

Example 78

[7S-(7alpha, 10aalpha)1-5-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-4-(cyclopropylamino)-5-oxopentanoic acid **(Formula I, R = 2-carboxylethyl, R^1 = H, W = cyclopropylamino)**

[0078] The titled compound is prepared by procedure of Example 6. The reactants are the product from Example 77 and cyclopropylamine.

[0079] Substantially following the method, described in detail herein above in Example 5, the compound of invention Example 79 is prepared.

Example 79

[4S-(4alpha, 12aalpha)]-9-[(Bromo (phenyl)acetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide **(Formula III, R = phenyl, R^1 = H, Y = Br,)**

Example 80

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[2-(dimethylamino)-2-phenylacetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R = phenyl, R^1 = H, W = dimethylamino)**

[0080] The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 79 and dimethylamine.

[0081] Substantially following the method, described in detail herein above in Example 5, the compound of invention Example 81 is prepared.

Example 81

[4S-(4alpha,12aalpha)1-9-[[Bromo(4-hydroxyphenyl)-acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide **(Formula III, R = 4-hydroxyphenyl, R^1 = H, Y = Br)**

Example 82

[4S-(4alpha,12aalpha)]-9-[[(Butylamino)(4-hydroxy-phenyl)acetyl]amino]4-(dimethylamino)-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R = 4-hydroxyphenyl, R^1 = H, W = butylamino)**

[0082] The titled compound is prepared by the procedure of Example 6.

[0083] Substantially following the method, described in detail herein above in Example 5, the compound of invention Example 83 is prepared.

Example 83

[4S-(4alpha,12aalpha)]-9-[[Bromo(4-methoxyphenyl)-acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide **(Formula III, R = 4-methoxyphenyl, R^1 = H, Y = Br)**

Example 84

[4S-(4alpha, 12aalpha)1-4-(Dimethylamino)-9-[[2-(dimethylamino)-2-(4-methoxyphenyl)acetyllaminol-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R = 4-methoxyphenyl, R^1 = H, W = dimethylamino)**

[0084] The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 83 and dimethylamine.

[0085] Substantially following the method, described in detail herein above in Example 5, the compound of invention Example 85 is prepared.

Example 85

[4S-(4alpha,12aalpha)]-9-[[Bromo[4-(trifluoromethyl)-phenyl]acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide **(Formula III, R = 4-trifluoromethylphenyl, R^1 = H, Y = Br)**

Example 86

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[2-(ethylmethylamino)-2-[4-(trifluoromethyl)phenyl]acetyl]aminol-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2 -naphthacenecarboxamide **(Formula I, R = 4-trifluoromethylphenyl, R^1 = H, W = N-ethylmethylamino)**

[0086] The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 85 and N-ethylmethylamine.

[0087] Substantially following the method, described in detail herein above in Example 5, the compound of invention Example 87 is prepared.

Example 87

[4S-(4alpha,12aalpha)]-9-[[Bromo[4-(dimethylamino)-phenyl]acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide **(Formula III, R = 4-(dimethylamino)phenyl, R^1 = H, Y = Br)**

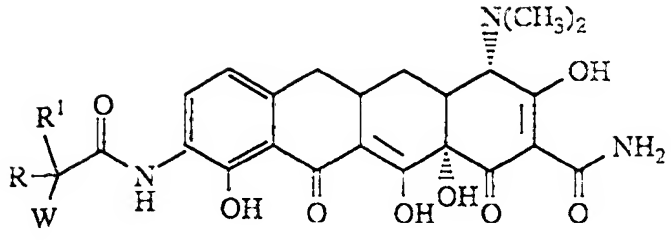
Example 88

[4S-(4alpha,12aalpha)1-4-(Dimethylamino)-9-[[[4-(dimethylamino)phenyl](2-propenylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R = 4-(dimethylamino)phenyl, R^1 = H, W = 2-propenylamino)**

[0088] The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 87 and N-allylamine.

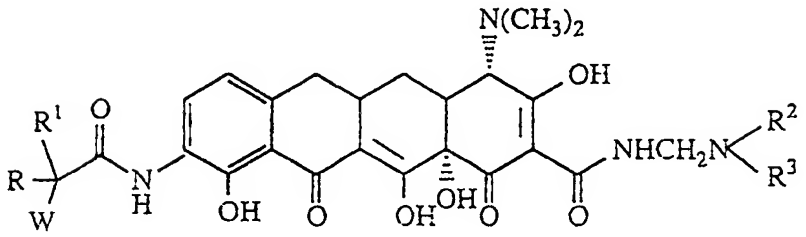
Claims

1. A compound of the formula:



(I)

or



(II)

wherein:

R is selected from

hydrogen;
straight or branched (C_1-C_8)alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl;
α-mercapto(C_1-C_4)alkyl group selected from mercaptomethyl, α-mercaptoethyl, α-mercapto-1-methylethyl, α-mercaptopropyl and α-mercaptobutyl;
α-hydroxy(C_1-C_4)alkyl group selected from hydroxymethyl, α-hydroxyethyl, α-hydroxy-1- methylethyl, α-hydroxypropyl and α-hydroxybutyl;
carboxyl(C_1-C_8)alkyl group;
(C_6-C_{10})aryl group selected from phenyl, α-naphthyl and β-naphthyl; or substituted(C_6-C_{10})aryl group (substitution selected from hydroxy, halogen, (C_1-C_4)alkoxy, trihalo(C_1-C_3) alkyl, nitro, amino, cyano, (C_1-C_4)alkoxycarbonyl, (C_1-C_3)alkylamino and carboxy);
(C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; or substituted (C_7-C_9)aralkyl group [substitution selected from halo, (C_1-C_4)alkyl, nitro, hydroxy, amino, mono- or di-substituted (C_1-C_4)alkylamino, (C_1-C_4)alkoxy, (C_1-C_4)alkylsulfonyl, cyano and carboxy];

R^1 is selected from hydrogen and (C_1-C_6)alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl; when R does not equal R^1 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D);

W is selected from

amino;
hydroxylamino;
(C_1-C_{12}) straight or branched alkyl monosubstituted amino group substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-di-methylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1-methyl-1-ethylpropyl, heptyl,

octyl, nonyl, decyl, undecyl and dodecyl and the diastereomers and enantiomers of said branched alkyl monosubstituted amino group;

(C_3-C_8)cycloalkyl monosubstituted amino group substitution selected from cyclopropyl, trans-1,2-dimethylcyclopropyl, cis-1,2-dimethylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1] hept-2-yl, and bicyclo[2.2.2]oct-2-yl and the diastereomers and enantiomers of said (C_3-C_8) cycloalkyl monosubstituted amino group;

[(C_4-C_{10})cycloalkyl]alkyl monosubstituted amino group substitution selected from (cyclopropyl)methyl, (cyclopropyl)ethyl, (cyclobutyl)methyl, (trans-2-methylcyclopropyl)methyl, and (cis-2-methylcyclobutyl) methyl;

(C_3-C_{10})alkenyl monosubstituted amino group substitution selected from allyl, 3-butenyl, 2-butenyl (cis or trans), 2-pentenyl, 4-octenyl, 2,3-dimethyl-2-butenyl, 3-methyl-2-butenyl, 2-cyclopentenyl and 2-cyclohexenyl;

(C_6-C_{10})aryl monosubstituted amino group substitution selected from phenyl and naphthyl;

(C_7-C_{10})aralkylamino group substitution selected from benzyl, 2-phenylethyl, 1-phenylethyl, 2-(naphthyl) methyl, 1-(naphthyl)methyl and phenylpropyl; substituted (C_6-C_{10})aryl monosubstituted amino group [substitution selected from (C_1-C_5)acyl, (C_1-C_5)acylamino, (C_1-C_4)alkyl, mono or disubstituted (C_1-C_8) alkylamino, (C_1-C_4)alkoxy, (C_1-C_4)alkoxycarbonyl, (C_1-C4)alkylsulfonyl, amino, carboxy, cyano, halogen, hydroxy, nitro and trihalo(C_1-C_3)alkyl];

straight or branched symmetrical disubstituted (C_2-C_{14})alkylamino group substitution selected from dimethyl, diethyl, diisopropyl, di-n-propyl, di-n-butyl and diisobutyl;

symmetrical disubstituted (C_3-C_{14})cycloalkylamino group substitution selected from dicyclopropyl, dicyclobutyl, dicyclopentyl, dicyclohexyl and dicycloheptyl;

straight or branched unsymmetrical disubstituted (C_3-C_{14})alkylamino group wherein the total number of carbons in the substitution is not more than 14;

unsymmetrical disubstituted (C_4-C_{14})cycloalkylamino group wherein the total number of carbons in the substitution is not more than 14;

(C_2-C_8)azacycloalkyl or substituted (C_2-C_8)azacycloalkyl group selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, 4-methylpiperidinyl, 2-methylpyrrolidinyl, cis-3,4-dimethylpyrrolidinyl, trans-3,4-dimethylpyrrolidinyl, 2-azabicyclo[2.1.1]hex-2-yl, 5-azabicyclo[2.1.1]hex-5-yl, 2-azabicyclo-[2.2.1]hept-2-yl, 7-azabicyclo[2.2.1]hept-7-yl, and 2-azabicyclo[2.2.2]oct-2-yl and the diastereomers and enantiomers of said (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)azacycloalkyl group;

1-azaoxacycloalkyl group selected from molpholinyl and 1-aza-5-oxacycloheptane; substituted 1-azaoxacycloalkyl group selected from 2-(C_1-C_3)alkylmorpholinyl, 3-(C_1-C_3)alkylisoxazolidinyl, tetrahydrooxazinyl and 3,4-dihydrooxazinyl;

[1 ,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group selected from piperazinyl, 2-(C_1-C_3) alkylpiperazinyl, 4-(C_1-C_3)alkylpiperazinyl, 2,4-dimethylpiperazinyl, 4-(C_1-C_4)alkoxypiperazinyl, 4-(C_6-C_{10})aryloxypiperazinyl, 4-hydroxypiperazinyl, 2,5-diazabicyclo-[2.2.1]hept-2-yl, 2,5-diaza-5-methylbicyclo-[2.2.1]hept-2-yl, 2,3-diaza-3- methylbicyclo-[2.2.2]oct-2-yl, and 2,5-diaza-5,7-dimethylbicyclo[2.2.2] oct-2-yl and the diastereomers or enantiomers of said [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group;

1-azathiacycloalkyl and substituted 1-azathiacycloalkyl group selected from thiomorpholinyl, 2-(C_1-C_3) alkythiomolpholinyl and 3-(C_3-C_6)cycloalkylthiomorpholinyl;

N-azolyl and substituted N-azolyl group selected from 1-imidazolyl, 2-(C_1-C_3)alkyl-1-imidazolyl, 3-(C_1-C_3) alkyl-1-imidazolyl, 1-pyrrolyl, 2-(C_1-C_3)alkyl-1-pyrrolyl, 3-(C_1-C_3)alkyl-1-pyrrolyl, 1-pyrazolyl, 3-(C_1-C_3) alkyl-1-pyrazolyl, indolyl, 1-(1,2,3-triazolyl), 4-(C_1-C_3)alkyl-1-(1,2,3-triazolyl), 5-(C_1-C_3)alkyl-1-(1,2,3-triazolyl), 4-(1,2,4-triazolyl), 1-tetrazolyl, 2-tetrazolyl and benzimidazolyl;

(heterocycle)amino group selected from 2- or 3-furanylamino, 2- or 3-thienylamino, 2-, 3- or 4-pyridylamino, 2- or 5-pyridazinylamino, 2-pyrazinylamino, 2-(imidazolyl)amino, (benzimidazolyl)amino, and (benzothiazolyl)amino and substituted (heterocycle)amino group as defined above with substitution selected from straight or branched (C_1-C_6)alkyl;

(heterocycle)methylamino group selected from 2- or 3-furylmethylamino, 2- or 3-thienylmethylamino, 2-, 3- or 4-pyridylmethylamino, 2- or 5-pyridazinylmethylamino, 2-pyrazinylmethylamino, 2-(imidazolyl)methylamino, (benzimidazolyl)methylamino, and (benzothiazolyl) methylamino and substituted (heterocycle) methylamino group as defined above with substitution selected from straight or branched (C_1-C_6)alkyl;

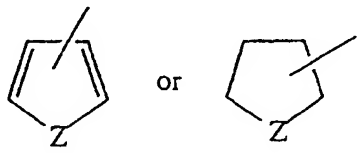
carboxy(C_2-C_4)alkylamino group selected from aminoacetic acid, α-aminopropionic acid, β-aminopropionic acid, α-aminobutyric acid, and β-aminobutyric acid and the enantiomers of said carboxy(C_2-C_4) alkylamino group;

(C_1-C_4)alkoxycarbonylamino group substitution selected from methoxycarbonyl, ethoxycarbonyl, allyloxy-

carbonyl, propoxycarbonyl, isoproproxycarbonyl, 1,1-dimethyl- ethoxycarbonyl, n-butoxycarbonyl, and 2-methylpropoxycarbonyl;
(C_1-C_4)alkoxyamino group substitution selected from methoxy, ethoxy, n-propoxy, 1-methylethoxy, n-butoxy, 2-methylpropoxy, and 1,1-dimethylethoxy;
(C_3-C_8)cycloalkoxyamino group substitution selected from cyclopropoxy, trans-1,2-dimethylcyclopropoxy, cis-1,2-dimethylcyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, cycloheptoxy, cyclooctoxy, bicyclo [2.2.1]hept-2-yloxy, and bicyclo[2.2.2]oct-2- yloxy and the diastereomers and enantiomers of said (C_3-C_8) cycloalkoxyamino group;
(C_6-C_{10})aryloxyamino group selected from phenoxyamine, 1-naphthyloxyamino and 2-naphthyloxyamine; and
(C_7-C_{11})arylalkoxyamino group substitution selected from benzyloxy, 2-phenylethoxy, 1-phenylethoxy, 2-(naphthyl)methoxy, 1-(naphthyl)methoxy and phenylpropoxy;

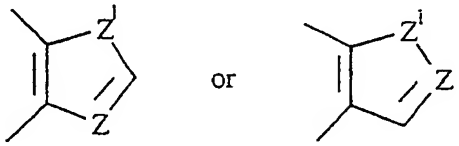
R^2 and R^3 are independently selected from

(i) hydrogen, providing that R^2 and R^3 are not both hydrogen;
(ii) straight or branched (C_1-C_3)-alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl;
(iii) (C_6-C_{10})aryl group selected from phenyl, α-naphthyl or β-naphthyl;
(iv) (C_7-C_9)aralkyl group;
(v) a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



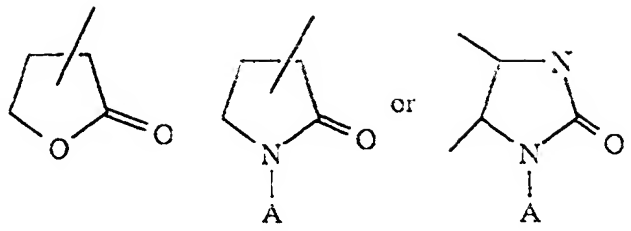
Z = N, O, S or Se

(vi) a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



Z or Z^1 = N, O, S or Se

(vii) a five membered satulated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(wherein A is selected from hydrogen; straight or branched (C_1-C_4)alkyl; C_6-aryl; substituted C_6-aryl (substitution selected from halo, (C_1-C_4)alkoxy, trihalo(C_1-C_3)alkyl, nitro, amino, cyano, (C_1-C_4)alkoxycarbonyl, (C_1-C_3)alkylamino or carboxy); benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl);
(viii) a six membered aromatic ring with one to three N heteroatoms,
(ix) a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom;
(x) -$(CH_2)_n$COOR^4 where n=0-4 and R^4 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl;
or
(xi) (C_6-C_{10})aryl group selected from phenyl, α-naphthyl, or β-naphthyl;

or **R^2 and R^3** taken together are

(i) -$(CH_2)_2B(CH_2)_2$-, wherein B is selected from $(CH_2)_n$ and n=0-1, -NH, -N(C_1-C_3)alkyl [straight or branched], -N(C_1-C_4)alkoxy, oxygen, sulfur;
or
(ii) substituted congeners selected from (L or D)proline and ethyl(L or D)prolinate, and the pharmacologically acceptable organic and inorganic salts or metal complexes.

2. The compound according to Claim 1,wherein:

R and **R^1** are independently selected from hydrogen, methyl or ethyl, and when R does not equal **R^1** the stereochemistry of the asymmetric carbon may be either the racemate (DL) or the individual enantiomers (L or D);

W is selected from amino, methylamino, ethylamino, n-propylamino, 1-methylethylamino, n-butylamino, 1-methylpropylamino, 2-methylpropylamino, n-hexylamino, n-octylamino, cyclopropylamino, cyclopentylamino, cyclohexylamino, (cyclopropyl)methylamino, (cyclopropyl)ethylamino, allylamino 3-butenylamino, benzylamino, 2-phenylethylamino, 1-phenylethylamino, dimethylamino, diethylamino, methyl(ethyl)amino; pyrrolidinyl, piperidinyl, morpholinyl, 2-(C_1-C_3)alkylmorpholinyl, piperazinyl, 2-(C_1-C_3)alkylpiperazinyl, 4-(C_1-C_3) alkylpiperazinyl, 2,5-diaza-5-methylbicyclo[2.2.1]hept-2-yl, (and the diastereomers or enantiomers of said [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group); thiomorpholinyl, 2-(C_1-C_3)alkylthiomorpholinyl, 1-imidazolyl, 2- or 3-thienylmethylamino, 2-, 3- or 4-pyridylmethylamino, methoxycarbonylamino, ethoxycarbonylamino, and 1,1-dimethylethoxycarbonylamino,

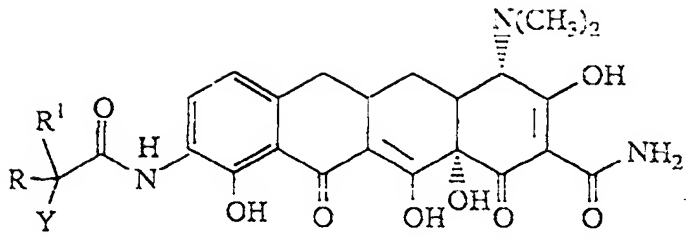
R^2 and **R^3** are independently selected from hydrogen, methyl, ethyl, n-propyl and 1-methylethyl; with the proviso that R^2 and R^3 cannot both be hydrogen;

or **R^2** and **R^3** taken together are

(i) -$(CH_2)_2B(CH_2)_2$-, wherein B is selected from $(CH_2)_n$ (wherein n=0-1), -NH, -N(C_1-C_3)alkyl [straight or branched], -N(C_1-C_4)alkoxy, oxygen, or sulfur
or (ii) substituted congeners selected from (L or D)proline and ethyl(L or D)prolinate;

and the pharmacologically acceptable organic and inorganic salts or metal complexes.

3. A compound of the formula:



(III)

wherein:

Y is selected from brornine, chlorine, fluorine or iodine;

R is selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl, octyl, mercaptomethyl, α-mercaptoethyl, a-mercapto-1-methylethyl, α-mercaptopropyl, α-mercaptobutyl, hydroxymethyl, α-hydroxyethyl, α-hydroxy-1-methylethyl, α-hydroxypropyl, α-hydroxybutyl; a carboxyl(C_1-C_8)alkyl group;

a phenyl, α-naphthyl or β-naphthyl group each optionally substituted by hydroxy, halogen, (C_1-C_4)alkoxy, trihalo(C_1-C_3) alkyl, nitro, amino, cyano, (C_1-C_4)alkoxycarbonyl, (C_1-C_3)alkylamino and carboxy;

or a benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl group each optionally substituted by:
halo, (C_1-C_4)alkyl, nitro, hydroxy, amino, mono- or di-substituted (C_1-C_4)alkylamino, (C_1-C_4)alkoxy, (C_1-C_4)alkylsulfonyl, cyano and carboxy];

R^1 is selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl; and when R does not equal R^1 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the Y substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salt or metal complexes.

4. The compound according to Claim 3,
wherein:

Y is selected from bromine, chlorine, fluorine and iodine;
R is selected from hydrogen, methyl or ethyl,
and
R^1 is selected from hydrogen, methyl or ethyl,
when R does not equal R^1 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the Y substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salt or metal complexes.

5. The compound according to Claim 1 wherein said salts comprise: hydrochloric, hydrobromic, hydroiodic, phosphoric, nitric, sulfate, acetate, benzoate, citrate, cysteine or other amino acid, fumarate, glycolate, maleate, succinate, tartrate, alkylsulfonate or arylsulfonate
and
said metal complexes comprise: aluminum, calcium, iron, magnesium, manganese and complex salts.

6. A compound according to Claim 1, which is one of the following

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[(hexyl-amino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-. naphthacenecarboxamide dihydrochloride **(Formula I, R and R^1 = H, W = n-hexylamino di HCl salt);**

[4S-(4alpha,12aalpha)]-4-(dimethyl)amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[

(methylamino)acetyl]amino]-1,11-dioxo-2-naphthacene-carboxamide dihydrochloride **(Formula I, R and R^1 = H, W = methylamino, di HCl salt);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[(ethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride **(Formula I, R and R^1 = H, W = ethylamino, di HCl salt);**

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-pyrrolidineacetamide dihydrochloride **(Formula I, R and R^1 = H, W = pyrrolidin-1-yl, di HCl salt);**

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-methyl-1-piperidineacetamide dihydrochloride **(Formula I, R and R^1 = H, W = 4-methylpiperidin-1-yl, di HCl salt);**

11[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(propylamino)acetyl]amino]-2-naphthacenecarboxamide dihydrochloride **(Formula I, R and R^1 = H, W = propylamino, di HCl salt);**

[4S-(4alpha, 12aalpha)]-9-[[(Butylamino)acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride **(Formula I, R and R^1 = H, W = n-butylamino, di HCl salt);**

[4S-(4alpha, 12aalpha)]-4-(Dimethylamino)-9-[[2-(dimethylamino)-1-oxopropyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride
(Formula I, R =CH_3, R^1 = H, W = dimethylamino, di HCl salt);

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,1 11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(pentylamino)acetyl]amino]-2-naphthacenecarboxamide monohydrochloride **(Formula I, R and R^1 = H, W = pentylamino, di HCl salt);**

[7S-(7alpha, 10aalpha)]-N-9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-1-piperidineacetamide dihydrochloride **(Formula I, R and R^1 = H, W = piperidino, di HCl salt);**

[4S-(4alpha, 12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,1-dioxo-9-[[[(phenylmethyl)amino]acetyl]amino]-2-naphthacenecarboxamide dihydrochloride
(Formula I, R and R^1 = H, W = benzylamino, di HCl salt);

[4S-(4alpha, 12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(2-thienylmethyl)amino]acetyl]amino]-2-naphthacenecarboxamide dihydrochloride **(Formula I, R and R^1 = H, W = thien-2-ylmethylamino, di HCl salt);**

[4S-(4alpha, 12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(2-methylpropyl)-amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride
(Formula I, R and R^1 = H, W = isobutylamino, di HCl salt);

[4S-(4alpha, 12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(2-pyridinylmethyl]amino]acetyl]amino]-2-naphthacenecarboxamide dihydrochloride
(Formula I, R and R^1 = H, W = pyridin-2-ylmethylamino, di HCl salt);

[4S-(4alpha,12aalpha)]-9-[[(Diethylamino)acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride **(Formula I, R and R^1 = H, W = diethylamino, di HCl salt);**

[7S-(7alpha, 10aalpha)]-N-9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-alpha-methyl-1-pyrrolidineacetamide(**Formula I, R=CH_3, R^1 = H, W = pyrrolidin-1-yl);**

[4S-(4alpha,12aalpha)]-9-[[[(Cyclopropylmethyl)amino]-acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride **(Formula I, R and R^1 = H, W = cyclopropylmethylamino, di HCl salt);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[(dimethyl-amino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate, dihydrochloride, monohydrochloride or free base **(Formula I, R and R^1 = H, W = dimethylamino) ;**

[4S-(4alpha, 12aalpha)]-4-(Dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-N-(1-pyrrolidinyl-methyl)-2-naphthacenecarboxamide **(Formula II, R and R^1 = H, W = NMe_2 and NR^2R^3 = pyrrolidino);**

[4S-(4alpha, 12aalpha)]-4-(Dimethylamino)- 1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[(methoxyamino)acetyl]amino]-1,11-dioxo-2-naphthacene-carboxamide **(Formula I, R and R^1 = H, W = methoxyamino);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(phenylmethoxy)amino]acetyl]amino]-2-naphthacenecarboxamide **(Formula I, R and R^1 = H, W = benzyloxyamino);**

[4S-(4alpha,12aalpha)]-9-[[(Cyclobutylmethylamino)-acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide **(Formula I, R and R^1 = H, W = cyclobutylmethyl-amino);**

[4S-(4alpha,12aalpha)]-9-[[(2-Butenylamino)acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R and R^1 = H, W =2-butenylamino);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)- 1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12α-tetrahydroxy-9-[[(hydroxyamino)acetyl]amino]-1,11-dioxo-2-naphthacene-carboxamide **(Formula I, R and R^1 = H, W = hydroxyamino);**

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)- 7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12dioxo-2-naphthacenyl]-5-methyl-2,5-diazabicyclo[2.2.1]heptane-2-acetamide **(Formula I, R and R^1 = H, W = 5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl);**

[75-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-3-methyl-4-morpholineacetamide **(Formula I, R and R^1 = H, W = 3-methyl-4-morpholinyl);**

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12dioxo-2-naphthacenyl]-2-azabicyclo[2.2.1]heptane-2-acetamide **(Formula I, R and R^1 = H, W = 2-azabicyclo[2.2.1]hept-2-yl);**

[7S-(7alpha, 10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12dioxo-2-naphthacenyl]-4-hydroxy-1-piperazineacetamide **(Formula I, R and R^1 = H, W = 4-hydroxypiperazin-1-yl));**

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12dioxo-2-naphthacenyl]-3-cyclopropyltetrahydro-4H-thiazine-4-acetamide **(Formula I, R and R^1 = H, W = 3-cyclopropyl-tetrahydro-4H-thiazin-4-yl));**

[7S-(7alpha, 10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12dioxo-2-naphthacenyl]-3-ethyl-1H-pyrrole-1-acetamide **(Formula I, R and R^1 = H, W = 3-ethyl-1H-pyrrol-1-yl));**

[4S-(4alpha.12aalpha)]-4-(Dimethylamino)- 1,4,4a,5,5a,6,11,12a-octahydro-3.10.12,12a-tetrahydroxy-9-[[(1H-imidazol-2-ylmethylamino)acetyl]amino)-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R and R^1 =**

H, W = 1H-imidazol-2-ylmethylamino);

[7S-(7alpha,10aalpha)]-N-[2-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-2-oxoethyl]alanine **(Formula I, R and R^1 = H, W = 1-carboxyethylamino);**

[7S-(7alpha,10aalpha)]-N-[2-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-2-oxoethyl]carbamic acid 1,1-dimethylethyl ester **(Formula I, R and R^1 = H, W = 1,1-dimethylethoxycarbonylamino);**

[4S-(4alpha,12aalpha)]-9-[[[(Bicyclo[2.2.2]oct-2-yloxy)amino]acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R and R^1 = H, W = bicyclo[2.2.2]oct-2-yloxyamino);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(3-methyl-2-butenyl) amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R and R^1 = H, W = 3-methyl-2-butenylamino);**

[4S-[4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[[4-[(2-methyl-1-oxopropyl)amino]phenyl]amino]acetyl]amino]-1,1-dioxo-2-naphthacenecarboxamide **(Formula I, R and R^1 = H, W = 4-[(2-methyl-1-oxopropyl)amino]phenylamino);**

[4S-(4alpha, 12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[2-[[(1-methyl-1H-imidazol-2-yl)methyl]amino]-1-oxopropyl]amino]-1,11-dioxo-2naphthacenecarboxamide **(Formula I, R = CH_3, R^1 = H, W = 1-methyl-1H-imidazol-2-yl)methylamino);**

[4S-(4alpha, 12aalyha)]-9-[[2-(Dicyclopropylamino)-1-oxopropyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,-11,12a-octahydro-3,10,12,12a-tetrahydroxy- 1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R = CH3, R^1 = H, W = dicyclopropylamino);**

[7S-(7alpha, 10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-10,12dioxo-2-naphthacenyl]-4-methoxy-α-methyl-1-piperazinecarboxamide **(Formula I, R = CH3, R^1 = H, W = 4-methoxypiperazin-1-yl);**

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12dioxo-2-naphthacenyl]-tetrahydro-α,2-dimethyl-4H-1,4-thiazine-4-acetamide **(Formula I, R = CH_3, R^1= H, W = tetrahydro-2-methyl-4H-1,4-thiazin-4-yl);**

[7S-(7alpha, 10aalpha)]-[2-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-2-oxo-1-methylethyl]carbamic acid 2-propenyl ester **(Formula I, R = CH_3, R^1 = H, W = 2-propenyloxycarbonylamino);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[2-[[3-(methylsulfonyl)phenyl]amino]-1-oxopropyl]amino]-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R = CH_3, R^1 = H, W = 3-(methylsulfonyl)phenylamino);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[2-methyl-2-(methylamino)-1-oxopropyl]amino]-1,1-dioxo-2-naphthacenecarboxamide **(Formula I, R and R^1 = Me, W = methylamino);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[2-(dimethylzmino)-2-methyl-1-oxopropyl]amilno]- 1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R and R^1 = Me, W = dimethylamino);**

[4S-(4alpha, 12aalpha)]-9-[[2-[(1,1-dimethylethyl)methylamino]-1-oxobutyl]amino]-4-(dimethylamino)-1.4,4a,5,5a,6,11,12a-octahydro-3,10,19,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R = Et, R^1 = H, W = N-methyl-t-butylamino);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[2-(dimethylamino)-3,3-dimethyl-1-oxobutyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R = ^{t}Bu, R^1 = H, W = dimethylamino);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[2-(ethylamino)-2-methyl-1-oxobutyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R = Et, R^1 = Me, W = ethylamino);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[2-(dimethylamino) -3-hydroxy-1-oxopropyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R = CH_2OH, R^1 - H, W = dimethylamino);**

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12dioxo-2-naphthacenyl]-α-(hydroxymethyl)-4-methyl-1H-imidazole-1-acetamide **(Formula I, R = CH_2OH, R^1 = H, W = 4-methyl-1H-imidazol-1-yl);**

[4S-(4alpha,12aalpha)]-9-[[2-(Diethylamino)-3-mercapto-1-oxopropyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R = mercaptomethyl, R^1 = H, W = dimethylamino);**

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12dioxo-2-naphthacenyl]-a-(mercaptomethyl)-1-piperazineacetamide **(Formula I, R = mercaptomethyl, R^1 = H, W = piperazin-1-yl);**

[7S-(7alpha, 10aalpha]-4-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-3-(hexylamino)-4-oxobutanoic acid **(Formula I, R = carboxymethyl, R^1 = H, W = hexylamino);**

[7S-(7alpha, 10aalpha)]-5-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a;6,6a,7,10;10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-4-(cyclopropylamino)-5-oxopentanoic acid **(Formula I, R = 2-carboxylethyl, R^1 = H, W = cyclopropylamino);**

[4S-(4alpha, 12aalpha)]-4-(Dimethylamino)-9-[[2-(dimethylamino)-2-phenylacetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R = phenyl, R^1 = H, W = dimethylamino) ;**

[4S-(4alpha,12aalpha)]-9-[[(Butylamino)(4-hydroxy-phenyl)acetyl]amino]4-(dimethylamino)-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R = 4-hydroxyphenyl, R^1 = H, W = butylamino);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[2-(dimethylamino)-2-(4-methoxyphenyl)acetyl] amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R = 4-methoxyphenyl, R^1 = H, W = dimethylamino);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[2-(ethylmethylamino)-2-[4-(trifluoromethyl)phenyl]acetyl]amino]- 1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R = 4-trifluoromethylphenyl, R^1 = H, W = N-ethylmethylamino); or**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[[4-(dimethylamino)phenyl](2-propenylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R = 4-(dimethylamino)phenyl, R^1 = H, W = 2-propenylamino).**

7. A compound which is one of the following:

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a-,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12dioxo-2-naphthacenyl]-4-ethyl-IH-pyrazole-1-acetamide, **(Formula I, R and R^1 = H, W = 4-ethyl-1H-pyrazol-1-yl);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[methyl(phenylmethyl)amino]acetyl]amino]-2-naphthacenecarboxamide,**(Formula I, R and R^1 = H, W = N-methylbenzylamino);**

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12dioxo-2-naphthacenyl]-6-methyl-2-azabicyclo[2.2.2]octane-2-acetamide, **(Formula I, R and R^1 = H, W = 6-methyl-2-azabicyclo[2.2.2]octan-2-yl);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[[(2-methylcyclopropyl)oxy]amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide **(Formula I, R and R^1 = H, W = (2-methylcyclopropyl)-oxyamino);**

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12dioxo-2-naphthacenyl]-3-ethyl-1-pyrrolidineacetamide, **(Formula I, R and R^1 = H, W = 3-ethylpyrrolidin-1-yl);**

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12dioxo-2-naphthacenyl]-4-(aminomethyl)-α-methyl-1-piperidineacetamide, **(Formula I, R = CH_3, R^1 = H, W = 4-aminomethylpiperidn-1-yl);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[2-[[(3-methylcyclobutyl)oxy]amino]-1-oxobutyl]amino]-1,11-dioxo-2-naphthacenecarboxamide hydrobromide, **(Formula I, R = H, R^1 = Et, W = 3-methylcyclobutyloxyamino);**

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12dioxo-2-naphthacenyl]-α-ethyl-4-methyl-2-isoxazolidineacetamide, **(Formula I, R = Et, R^1 = H, W = 4-methyl-isoxazolidin-2-yl);**

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-a-ethyl-3-methyl-4H-1,2,4-triazole-4-acetamide, **(Formula I, R = Et, R^1 = H, W = 3-methyl-4H-1,2,4-triazol-4-yl);**
or

[7S-(7alpha,10aalpha)]-4-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-3-[ethyl(phenylmethyl)amino]-4-oxobutanoic acid **(Formula I, R = carboxymethyl, R^1 = H, W = N-ethylbenzylamino).**

8. A compound according to Claim 3, which is one of the following

[4S-(4α,12aα)]-9-[(bromoacetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride**(Formula III, R and R^1=H, Y is Br, HCl salt);**

[4S-(4α,12aα)]-9-[(chloroacetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride**(Formula III, R and R^1=H, Y is Cl, HCl salt);**

[4S-(4α,12aα)]-9-[(bromoacetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrobromide**(Formula III, R and R^1=H, Y is Br, HBr salt);**

[4S-(4α,12aα)]-9-[(bromoacetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monosulfate**(Formula III, R and R^1=H, Y is Br, monosulfate salt);**

[4S-(4α, 12aα)]-9-[(2-bromo-1-oxopropyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrobromide **(Formula III, R = CH_3, R^1 = H, Y is Cl, HBr salt);**

[4S-(4α,12aα)]-9-[(2-Bromo-2-methyl-1-oxopropyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide(**Formula III, R and R^1 = CH_3, Y = Br);**

[4S-(4α,12aα)]-9-[(2-Bromo-1-oxobutyl)amino]- 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide hydrobromide **(Formula III, R = Et, R^1 = H, Y = Br);**

[4S-(4α,12aα)]-9-[(2-Bromo-1-oxopentyl)amino]- 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide hydrobromide **(Formula III R = Pr, R^1 = H, Y = Br);**

[4S-(4α,12aα)]-9-[(2-Bromo-2-methyl-1-oxobutyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide **(Formula III, R = Et, R^1 = Me, Y = Br)** ;

[4S-(4α,12aα)]-9-[(2-Bromo-3-hydroxy-1-oxopropyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide **(Formula III, R = Et, R^1 = Me, Y = Br);**

[4S-(4α,12aα)]-9-[(2-Bromo-3-mercapto- 1-oxopropyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,- 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide **(Formula III, R = mercaptomethyl, R^1 = H, Y=Br);**

[7S-(7α, 10aα)]4-[[9-(Aminocarbonyl)- 7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro- 1,8,10a,11-tetrahydroxy-10-12-dioxo-2-naphthacenyl]amino]-3-bromo-4-oxobutanoic acid hydrobromide **(Formula III, R = carboxymethyl, R^1 = H, Y = Br,);**

[7S-(7α, 10aα)]-5-[[9-(Aminocarbonyl)- 7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-4-bromo-5-oxopentanoic acid hydrobromide(**Formula III, R = 2-carboxyethyl, R^1 = H, Y = Br,);**

[4S-(4α, 12aα)]-9-[(Bromophenylacetyl)arnino]- 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide hydrobromide(**Formula III, R = phenyl, R^1 = H, Y = Br);**

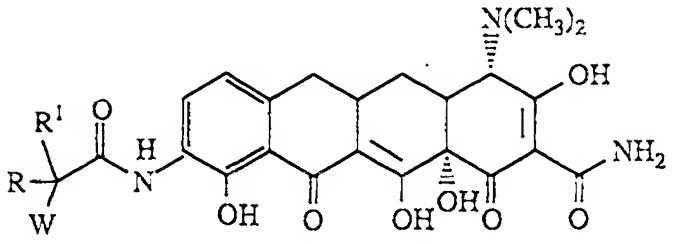
[4S-(4α,12aα)]-9-[[Bromo(4-hydroxyphenyl)acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo- 2-naphthacenecarboxamide hydrobromide **(Formula III, R = 4-hydroxyphenyl, R^1 = H, Y = Br);**

[4S-(4α,12aα)]-9-[[Bromo(4-methoxyphenyl)acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide **(Formula III, R = 4-methoxyphenyl, R^1 = H, Y = Br);**

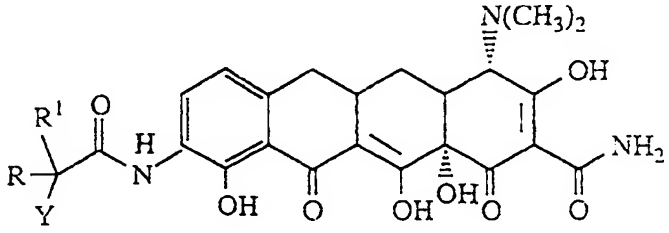
[4S-(4α,12aα)]-9-[[Bromo[4-(trifluoromethyl)phenyl]acetyl]amino]-4-(dimethylamino)-14,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide **(Formula III, R = 4-trifluoromethylphenyl, R^1=H, Y=Br);**
and

[4S-(4α,12aα)]-9-[[Bromo[4-(dimethylamino)phenyl]acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12.12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide **(Formula III, R = 4-(dimethylamino)phenyl, R^1 = H, Y = Br).**

9. A method of producing a compound, or its organic and inorganic salt or metal complex, of the formula:

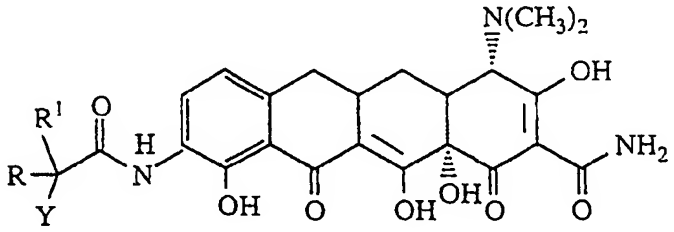


according to Claim 1, which comprises reacting a 9-[(haloacyl)amido]-6-demethyl-6-deoxytetracycline, or its organic and inorganic salt or metal complex, of the formula:

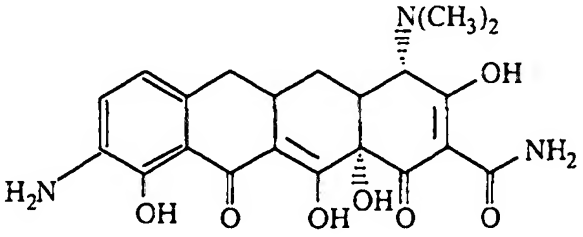


according to Claim 3, With a nucleophile of the formula WH, wherein W is as defined in Claim 1. in a polar-aprotic solvent and in an inert atmosphere.

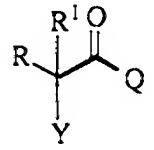
10. A method of producing a compound, or its organic and inorganic salt or metal complex, of the formula:



according to Claim 3, which comprises reacting 9-amino-6-demethyl-6-deoxytetracycline, or its organic and inorganic salt or metal complex, of the formula:

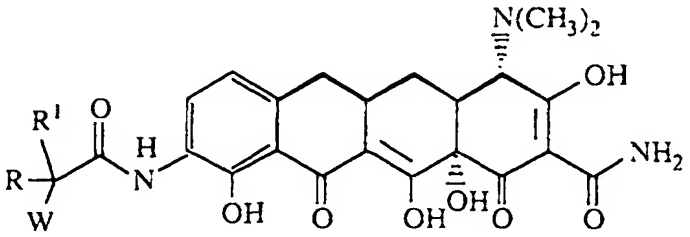


with a straight or branched haloacyl halide of the formula:

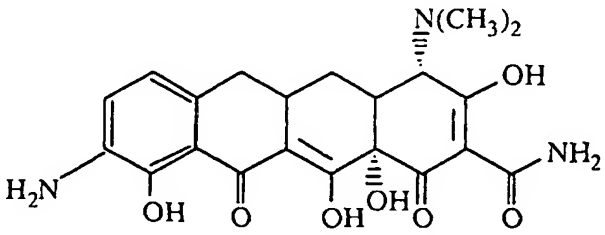


wherein Y, R and R^1 are as defined in Claim 3 and Q is halogen selected from bromine, chloride, iodine and fluorine, in an inert solvent in a polar-aprotic solvent and in the presence of a base.

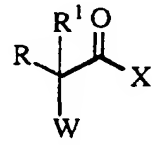
11. A method of producing a compound, or its organic and inorganic salt or metal complex, of the formula:



according to Claim 1, which comprises reacting a 9-amino-6-demethyl-6-deoxytetracycline, or its organic and inorganic salt or metal complex, of the formula:



with an acid halide of the formula:



wherein R, R^1, and W are as defined in Claim 1 and X is selected from bromine, chlorine, iodine and fluorine, in an inert solvent in a polar-aprotic solvent and in the presence of a base.

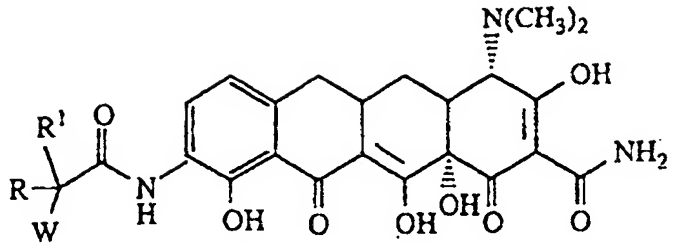
12. Use of a compound as claimed in any one of claims 1, 2, 5, 6 or 7 in the preparation of a medicament for the prevention, treatment or control of bacterial infections in warm-blooded animals.

13. A pharmaceutical composition of matter comprising a pharmacologically effective amount of a compound according to Claim 1, 2, 5, 6 or 7 in association with a pharmaceutically acceptable carrier.

14. A veterinary composition which comprises a pharmacologically effective amount of a compound of Claim 1, 2, 5, 6 or 7 and a pharmaceutically acceptable carrier.

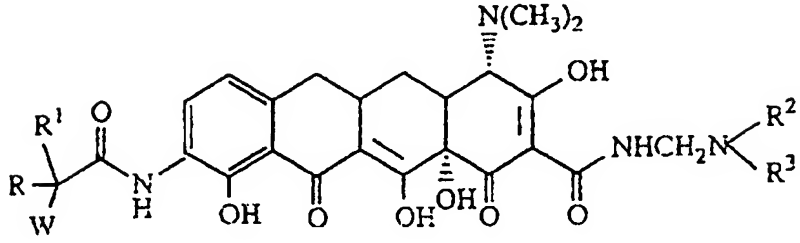
Patentansprüche

1. Verbindung der Formel:



(I)

oder



(II)

worin **R** ausgewählt wird aus

Wasserstoff;
grader oder verzweigter (C_1-C_8)Alkylgruppe, ausgewählt aus Methyl, Ethyl, Propyl, Isopropyl, Butyl, Isobutyl, Pentyl, Hexyl, Heptyl und Octyl;
α-Mercapto(C_1-C_4)alkylgruppe, ausgewählt aus Mercaptomethyl, α-Mercaptoethyl, a-Mercapto-1-methylethyl, α-Mercaptopropyl und α-Mercaptobutyl;
α-Hydroxy(C_1-C_4) alkylgruppe, ausgewählt aus Hydroxymethyl, α-Hydroxyethyl, α-Hydroxy-1-methylethyl, α-Hydroxypropyl und α-Hydroxybutyl;
Carboxyl(C_1-C_8)alkylgruppe;
(C_6-C_{10})Arylgruppe, ausgewählt aus Phenyl, α-Naphthyl und β-Naphthyl; oder substituierter (C_6-C_{10})Arylgruppe (Substitution ausgewählt aus Hydroxy, Halogen, (C_1-C_4)Alkoxy, Trihalogen(C_1-C_3)alkyl, Nitro, Amino, Cyano, (C_1-C_4)Alkoxycarbonyl, (C_1-C_3)-Alkylamino und Carboxy);
(C_7-C_9)Aralkylgruppe, ausgewählt aus Benzyl, 1-Phenylethyl, 2-Phenylethyl und Phenylpropyl; oder substituierter (C_7-C_9)-Aralkylgruppe [Substitution ausgewählt aus Halogen, (C_1-C_4)Alkyl, Nitro, Hydroxy, Amino, mono- oder disubstituiertem (C_1-C_4)Alkylamino, (C_1-C_4)Alkoxy, (C_1-C_4)Alkylsulfonyl, Cyano und Carboxy] ;

R^1 ausgewählt wird aus Wasserstoff und (C_1-C_6)Alkyl, ausgewählt aus Methyl, Ethyl, Propyl, Isopropyl, Butyl, Isobutyl, Pentyl und Hexyl; wenn R nicht gleich R^1, kann die Stereochemie des asymmetrischen Kohlenstoffs (also des Kohlenstoffs, der den W-Substituenten trägt) entweder das Racemat (DL) oder das einzelne Enantiomer (L oder D) sein;
W ausgewählt wird aus:

Amino;
Hydroxylamino;
(C_1-C_{12}) grader oder verzweigter Alkyl-monosubstituierter Aminogruppe, wobei die Substitution ausgewählt wird aus Methyl, Ethyl, n-Propyl, 1-Methylethyl, n-Butyl, 1-Methylpropyl, 2-Methylpropyl, 1,1-Dime-

thylethyl, n-Pentyl, 2-Methylbutyl, 1,1-Dimethylpropyl, 2,2-Dimethylpropyl, 3-Methylbutyl, n-Hexyl, 1-Methylpentyl, 1,1-Dimethylbutyl, 2,2-Dimethylbutyl, 3-Methylpentyl, 1,2-Dimethylbutyl, 1,3-Dimethylbutyl, 1-Methyl-1-ethylpropyl, Heptyl, Octyl, Nonyl, Decyl, Undecyl und Dodecyl und den Diastereomeren und Enantiomeren der besagten verzweigten Alkylmonosubstituierten Aminogruppe;

(C_3-C_8)Cycloalkyl-monosubstituierter Aminogruppe, wobei die Substitution ausgewählt wird aus Cyclopropyl, trans-1,2-Dimethylcyclopropyl, cis-1,2-Dimethylcyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Cycloheptyl, Cyclooctyl, Bicyclo-[2.2.1]hept-2-yl und Bicyclo[2.2.2]oct-2-yl und den Diastereomeren und Enantiomeren der besagten (C_3-C_8)Cycloalkyl-monosubstituierter Aminogruppe;

[(C_4-C_{10})Cycloalkyl]alkyl-monosubstituierter Aminogruppe, wobei die Substitution ausgewählt wird aus (Cyclopropyl)methyl, (Cyclopropyl)ethyl, (Cyclobutyl)methyl, (trans-2-Methylcyclopropyl)methyl und (cis-2-Methylcyclobutyl)methyl;

(C_3-C_{10})Alkenyl-monosubstituierter Aminogruppe, wobei die Substitution ausgewählt wird aus Allyl, 3-Butenyl, 2-Butenyl (cis oder trans), 2-Pentenyl, 4-Octenyl, 2,3-Dimethyl-2-butenyl, 3-Methyl-2-butenyl, 2-Cyclopentenyl und 2-Cyclohexenyl;

(C_6-C_{10})Aryl-monosubstituierter Aminogruppe, wobei die Substitution ausgewählt wird aus Phenyl und Naphthyl;

(C_7-C_{10})Aralkylaminogruppe, wobei die Substitution ausgewählt wird aus Benzyl, 2-Phenylethyl, 1-Phenylethyl, 2-(Naphthyl)methyl, 1-(Naphthyl)methyl und Phenylpropyl;

substituierter (C_6-C_{10})Aryl-monosubstituierter Aminogruppe [wobei die Substitution ausgewählt wird aus (C_1-C_5)Acyl, (C_1-C_5)-Acylamino, (C_1-C_4)Alkyl, mono- oder disubstituiertem (C_1-C_8)-Alkylamino, (C_1-C_4) Alkoxy, (C_1-C_4)Alkoxycarbonyl, (C_1-C_4)Alkylsulfonyl, Amino, Carboxy, Cyano, Halogen, Hydroxy, Nitro und Trihalogen(C_1-C_3)alkyl];

grader oder verzweigter, symmetrisch disubstituierter (C_2-C_{14})Alkylaminogruppe, wobei die Substitution ausgewählt wird aus Dimethyl, Diethyl, Diisopropyl, Di-n-propyl, Di-n-butyl und Diisobutyl;

symmetrisch disubstituierter (C_3-C_{14})Cycloalkylaminogruppe, wobei die Substitution ausgewählt wird aus Dicyclopropyl, Dicyclobutyl, Dicyclopentyl, Dicyclohexyl und Dicycloheptyl;

grader oder verzweigter, unsymmetrisch disubstituierter (C_3-C_{14})Alkylaminogruppe, wobei die Gesamtzahl an Kohlenstoffen in der Substitution nicht mehr als 14 beträgt;

unsymmetrisch disubstituierter (C4-C14)Cycloalkylaminogruppe, wobei die Gesamtzahl an Kohlenstoffen in der Substitution nicht mehr als 14 beträgt;

(C_2-C_8)Azacycloalkyl oder substituierter (C2-C8)Azacycloalkylgruppe, ausgewählt aus Aziridinyl, Azetidinyl, Pyrrolidinyl, Piperidinyl, 4-Methylpiperidinyl, 2-Methylpyrrolidinyl, cis-3,4-Dimethylpyrrolidinyl, trans-3,4-Dimethylpyrrolidinyl, 2-Azabicyclo[2.1.1]hex-2-yl, 5-Azabicyclo[2.1.1]hex-5-yl, 2-Azabicyclo-[2.2.1]hept-2-yl, 7-Azabicyclo[2.2.1]hept-7-yl und 2-Azabicyclo[2.2.2]oct-2-yl und den Diastereomeren und Enantiomeren der besagten (C_2-C_8)Azacycloalkyl- und substituierten (C_2-C_8)Azacycloalkylgruppe;

1-Azaoxacycloalkylgruppe, ausgewählt aus Morpholinyl und 1-Aza-5-oxacycloheptan; substituierter 1-Azaoxacycloalkylgruppe, ausgewählt aus 2-(C_1-C_3)Alkylmorpholinyl, 3-(C_1-C_3)Alkylisoxazolidinyl, Tetrahydrooxazinyl und 3,4-Dihydrooxazinyl;

[1,n]-Diazacycloalkyl- und substituierter [1,n]-Diazacycloalkylgruppe, ausgewählt aus Piperazinyl, 2-(C_1-C_3)Alkylpiperazinyl, 4-(C_1-C_3)Alkylpiperazinyl, 2,4-Dimethylpiperazinyl, 4-(C_1-C_4)Alkoxypiperazinyl, 4-(C_6-C_{10})Aryloxypiperazinyl, 4-Hydroxypiperazinyl, 2,5-Diazabicyclo-[2.2.1]hept-2-yl, 2,5-Diaza-5-methylbicyclo-[2.2.1]hept-2-yl, 2,3-Diaza-3-methylbicyclo[2.2.2]oct-2-yl und 2,5-Diaza-5,7-dimethylbicyclo [2.2.2]oct-2-yl und den Diastereomeren oder Enantiomeren der besagten [1,n]-Diazacycloalkyl und substituierten [1,n]-Diazacycloalkylgruppe;

1-Azathiacycloaklyl und substituierter 1-Azathiacycloalkylgruppe, ausgewählt aus Thiomorpholinyl, 2-(C_1-C_3)Alkylthiomorpholinyl und 3-(C_3-C_6)Cycloalkylthiomorpholinyl;

N-Azolyl und substituierter N-Azolylgruppe, ausgewählt aus 1-Imidazolyl, 2-(C_1-C_3)Alkyl-1-imidazolyl, 3-(C_1-C_3)Alkyl-1-imidazolyl, 1-Pyrrolyl, 2-(C_1-C_3)Alkyl-1-pyrrolyl, 3-(C_1-C_3)Alkyl-1-pyrrolyl, 1-Pyrazolyl, 3-(C_1-C_3)Alkyl-1-pyrazolyl, Indolyl, 1-(1,2,3-Triazolyl), 4-(C_1-C_3)Alkyl-1-(1,2,3-triazolyl), 5-(C_1-C_3)Alkyl-1-(1,2,3-triazolyl), 4-(1,2,4-Triazolyl), 1-Tetrazolyl, 2-Tetrazolyl und Benzimidazolyl;

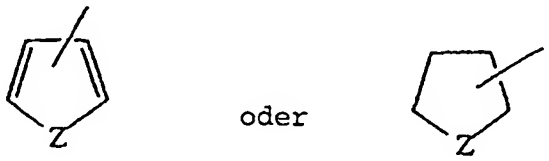
(heterocyclischer) Aminogruppe, ausgewählt aus 2- oder 3-Furanylamino, 2- oder 3-Thienylamino, 2-, 3- oder 4-Pyridylamino, 2- oder 5-Pyridazinylamino, 2-Pyrazinylamino, 2-(Imidazolyl)amino, (Benzimidazolyl)amino und (Benzothiazolyl)amino und substituierter (heterocyclischer) Aminogruppe, wie oben definiert, wobei die Substitution ausgewählt wird aus gradem oder verzweigtem (C_1-C_6)Alkyl;

(heterocyclischer) Methylaminogruppe, ausgewählt aus 2-oder 3-Furylmethylamino, 2- oder 3-Thienylmethylamino, 2-, 3-oder 4-Pyridylmethylamino, 2- oder 5-Pyridazinylmethylamino, 2-Pyrazinylmethylamino, 2-(Imidazolyl)methylamino, (Benzimidazolyl)methylamino und (Benzothiazolyl)methylamino und substituierter (heterocyclischer) Methylaminogruppe, wie oben definiert, wobei die Substitution ausgewählt

wird aus gradem oder verzweigtem (C_1-C_6)Alkyl:
Carboxy(C_2-C_4)Alkylaminogruppe, ausgewählt aus Aminoessigsäure, α-Aminopropionsäure, β-Aminopropionsäure, α-Aminobuttersäure und β-Aminobuttersäure und den Enantiomeren der besagten Carboxy (C_2-C_4)Alkylaminogruppe;
(C_1-C_4)Alkoxycarbonylaminogruppe, wobei die Substitution ausgewählt wird aus Methoxycarbonyl, Ethoxycarbonyl, Allyloxycarbonyl, Propoxycarbonyl, Isopropoxycarbonyl, 1,1-Dimethylethoxycarbonyl, n-Butoxycarbonyl und 2-Methylpropoxycarbonyl;
(C_1-C_4)Alkoxyaminogruppe, wobei die Substitution ausgewählt wird aus Methoxy, Ethoxy, n-Propoxy, 1-Methylethoxy, n-Butoxy, 2-Methylpropoxy und 1,1-Dimethylethoxy;
(C_3-C_8)Cycloalkoxyaminogruppe, wobei die Substitution ausgewählt wird aus Cyclopropoxy, trans-1,2-Dimethylcyclopropoxy, cis-1,2-Dimethylcyclopropoxy, Cyclobutoxy, Cyclopentoxy, Cyclohexoxy, Cycloheptoxy, Cyclooctoxy, Bicyclo[2.2.1]hept-2-yloxy und Bicyclo[2.2.2]oct-2-yloxy und den Diastereomeren und Enantiomeren der besagten (C_3-C_8)Cycloalkoxyaminogruppe;
(C_6-C_{10})Aryloxyaminogruppe, ausgewählt aus Phenoxyamino, 1-Naphthyloxyamino und 2-Naphthyloxyamino; und
(C_7-C_{11})Arylalkoxyaminogruppe, wobei die Substitution ausgewählt wird aus Benzyloxy, 2-Phenylethoxy, 1-Phenylethoxy, 2-(Naphthyl)methoxy, 1-(Naphthyl)methoxy und Phenylpropoxy;

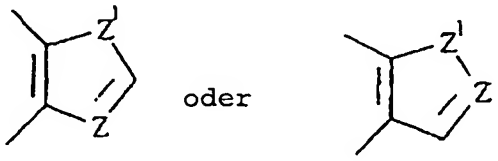
R^2 und **R^3** unabhängig ausgewählt werden aus

(i) Wasserstoff, vorausgesetzt, dass R^2 und R^3 nicht beide Wasserstoff darstellen;
(ii) grader oder verzweigter (C_1-C_3)-Alkylgruppe, ausgewählt aus Methyl, Ethyl, n-Propyl oder 1-xethylethyl;
(iii) (C_6-C_{10})Arylgruppe, ausgewählt aus Phenyl, α-Naphthyl oder β-Naphthyl;
(iv) (C_7-C_9)Aralkylgruppe;
(v) einer heterocyclischen Gruppe, ausgewählt aus einem aromatischen oder gesättigten Ring mit fünf Gliedern mit einem N-, O-, S- oder Se-Heteroatom, gegebenenfalls mit einem daran kondensierten Benzo- oder Pyridoring:



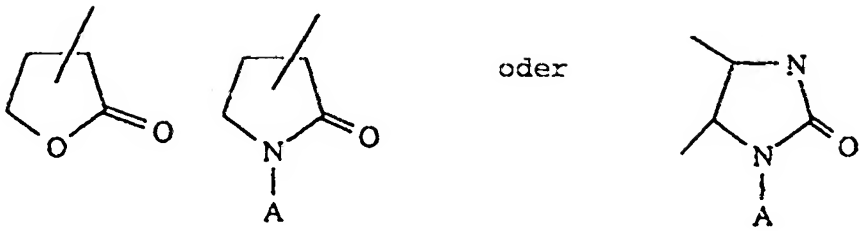
Z = N, O, S oder Se

(vi) einem aromatischen Ring mit fünf Gliedern mit zwei N-, O-, S- oder Se-Heteroatomen, gegebenenfalls mit einem daran kondensierten Benzo- oder Pyridoring:



Z oder Z^1 = N, O, S oder Se

(vii) einem aromatischen Ring mit fünf Gliedern mit ein oder zwei N-, O-, S- oder Se-Heteroatomen und einem angrenzend angehängten O-Heteroatom:



(worin A ausgewählt wird aus Wasserstoff: gradem oder verzweigtem (C_1-C_4)Alkyl; C_6-Aryl; substituiertem C_6-Aryl (Substitution ausgewählt aus Halogen, (C_1-C_4)Alkoxy, Trihalogen(C_1-C_3)alkyl, Nitro, Amino, Cyano, (C_1-C_4)Alkoxycarbonyl, (C_1-C_3)Alkylamino oder Carboxy); Benzyl, 1-Phenylethyl, 2-Phenylethyl oder PhenylproPYl);
(viii) einem aromatischen Ring mit sechs Gliedern mit einem bis drei N-Heteroatomen;
(ix) einem gesättigten Ring mit sechs Gliedern mit ein oder zwei N-, O-, S- oder Se-Heteroatomen und einem angrenzend angehängten O-Heteroatom;
(x) -$(CH_2)_n$COOR^4, worin n = 0-4 und R^4 ausgewählt wird aus Wasserstoff; grader oder verzweigter (C_1-C_3)Alkylgruppe, ausgewählt aus Methyl, Ethyl, n-Propyl oder 1-Methylethyl; oder
(xi) (C_6-C_{10})Arylgruppe, ausgewählt aus Phenyl, α-Naphthyl oder β-Naphthyl;

oder **R^2** und **R^3** zusammengenommen

(i) -$(CH_2)_2B(CH_2)_2$- darstellen, worin B ausgewählt wird aus $(CH_2)_n$ und n = 0-1, -NH, -N(C_1-C_3)Alkyl [grade oder verzweigt], -N(C_1-C4)Alkoxy, Sauerstoff, Schwefel; oder
(ii) substituierte verwandte Substanzen, ausgewählt aus (L oder D)Prolin und Ethyl(L oder D)prolinat, und die pharmakologisch annehmbaren organischen und anorganischen Salze oder Metallkomplexe.

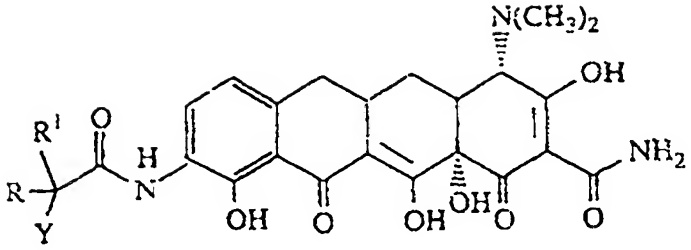
2. Verbindung gemäss Anspruch 1, worin:

R und **R^1** unabhängig ausgewählt werden aus Wasserstoff, Methyl oder Ethyl, und wenn R nicht das gleiche wie R^1 darstellt, kann die Stereochemie des asymmetrischen Kohlenstoffs entweder das Racemat (DL) oder das einzelne Enantiomer (L oder D) sein;
W ausgewählt wird aus Amino, Methylamino, Ethylamino, n-Propylamino, 1-Methylethylamino, n-Butylamino, 1-Methylpropylamino, 2-Methylpropylamino, n-Hexylamino, n-Octylamino, Cyclopropylamino, Cyclopentylamino, Cyclohexylamino, (Cyclopropyl)methylamino, (Cyclopropyl)ethylamino, Allylamino, 3-Butenylamino, Benzylamino, 2-Phenylethylamino, 1-Phenylethylamino, Dimethylamino, Diethylamino, Methyl(ethyl)amino; Pyrrolidinyl, Piperidinyl, Morpholinyl, 2-(C_1-C_3)Alkylmorpholinyl, Piperazinyl, 2-(C_1-C_3)Alkylpiperazinyl, 4-(C_1-C_3)Alkylpiperazinyl, 2,5-Diaza-5-methylbicyclo[2.2.1]hept-2-yl (und den Diastereomeren oder Enantiomeren von besagter [1,n]-Diazacycloalkyl- und substituierter [1,n]-Diazacycloalkylgruppe); Thiomorpholinyl, 2-(C_1-C_3)Alkylthiomorpholinyl, 1-Imidazolyl, 2- oder 3-Thienylmethylamino, 2-, 3- oder 4-Pyridylmethylamino, Methoxycarbonylamino, Ethoxycarbonylamino und 1,1-Dimethylethoxycarbonylamino,
R^2 und **R^3** unabhängig ausgewählt werden aus Wasserstoff, Methyl, Ethyl, n-Propyl und 1-Methylethyl; unter der Voraussetzung, dass R^2 und R^3 nicht beide Wasserstoff darstellen können; oder
oder **R^2** und **R^3** zusammengenommen

(i) -$(CH_2)_2B(CH_2)_2$- darstellen, worin B ausgewählt wird aus $(CH_2)_n$ (worin n = 0-1), -NH, -N(C_1-C_3)Alkyl [grade oder verzweigt], -N(C_1-C_4)Alkoxy, Sauerstoff oder Schwefel; oder
(ii) substituierte verwandte Substanzen, ausgewählt aus (L oder D)Prolin und Ethyl(L oder D)prolinat;

und die pharmakologisch annehmbaren organischen und anorganischen Salze oder Metallkomplexe.

3. Verbindung der Formel



(III)

worin:

Y ausgewählt wird aus Brom, Chlor, Fluor oder Iod;
R ausgewählt wird aus Wasserstoff, Methyl, Ethyl, Propyl, Isopropyl, Butyl, Isobutyl, Pentyl, Hexyl, Heptyl, Octyl, Mercaptomethyl, α-Mercaptoethyl, α-Mercapto-1-methylethyl, α-Mercaptopropyl, α-Mercaptobutyl, Hydroxymethyl, α-Hydroxyethyl, α-Hydroxy-1-methylethyl, α-Hydroxypropyl, α-Hydroxybutyl; einer Carboxyl(C_1-C_8)alkylgruppe; einer Phenyl-, α-Naphthyl oder β-Naphtylgruppe, jedes gegebenenfalls substituiert durch Hydroxy, Halogen, (C_1-C_4)Alkoxy, Trihalogen (C_1-C_3) alkyl, Nitro, Amino, Cyano, (C_1-C_4)Alkoxycarbonyl, (C_1-C_3)Alkylamino und Carboxy;
oder einer Benzyl-, 1-Phenylethyl-, 2-Phenylethyl- oder Phenylpropylgruppe, jede gegebenenfalls substituiert durch:
Halogen, (C_1-C_4)Alkyl, Nitro, Hydroxy, Amino, mono- oder disubstituiertem (C_1-C_4)Alkylamino, (C_1-C_4)Alkoxy, (C_1-C_4)Alkylsulfonyl, Cyano und Carboxy;
R^1 ausgewählt wird aus Wasserstoff, Methyl, Ethyl, Propyl, Isopropyl, Butyl, Isobutyl, Pentyl und Hexyl; und wenn R nicht das gleich wie R^1 darstellt, kann die Stereochemie des asymmetrischen Kohlenstoffs (also des Kohlenstoffs, der den Y-Substituenten trägt) entweder das Racemat (DL) oder die einzelnen Enantiomere (L oder D) sein; und die pharmakologisch annehmbaren organischen und anorganischen Salze oder Metallkomplexe.

4. Verbindung gemäss Anspruch 3, worin:

Y ausgewählt wird aus Brom, Chlor, Fluor und Iod;
R ausgewählt wird aus Wasserstoff, Methyl oder Ethyl und
R^1 ausgewählt wird aus Wasserstoff, Methyl oder Ethyl, und wenn R nicht das gleich wie R^1 darstellt, kann die Stereochemie des asymmetrischen Kohlenstoffs (also des Kohlenstoffs, der den Y-Substituenten trägt) entweder das Racemat (DL) oder die einzelnen Enantiomere (L oder D) sein; und die pharmakologisch annehmbaren organischen und anorganischen Salze oder Metallkomplexe.

5. Verbindung gemäss Anspruch 1, wobei besagte Salze umfassen: Chlorwasserstoff-, Bromwasserstoff-, Iodwasserstoff-, Phosphor-, Salpeter-, Sulfat-, Acetat-, Benzoat-, Citrat-, Cystein- oder andere Aminosäuren, Fumarat, Glycolat, Maleat, Succinat, Tartrat, Alkylsulfonat oder Arylsulfonat und
besagte Metallkomplexe umfassen: Aluminium-, Calcium-, Eisen-, Magnesium-, Mangan- und Komplexsalze.

6. Verbindung gemäss Anspruch 1, welche eine der folgenden ist:

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[(hexyl-amino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid Dihydrochlorid **(Formel I, R und R^1 = H, W = n-Hexylamino Di-HCl-Salz)**;
[4S-(4alpha,12aalpha)]-4-(Dimethyl)amino)-1,4,4a,5,5a,6, 11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[(methylamino)-acetyl]amino]-1,11-dioxo-2-naphthacencarboxamid Dihydrochlorid **(Formel I, R und R^1 = H, W = Methylamino, Di-HCl-Salz)** ;
[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[(ethylamino)-acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid Dihydrochlorid **(Formel I, R und R^1 = H, W = Ethylamino, Di-HCl-Salz)** ;
[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a-

11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-pyrrolidinacetamid Dihydrochlorid **(Formel I, R and R^1 = H, W = Pyrrolidin-1-yl, Di-HCl-Salz);**

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-methyl-1-piperidinacetamid Dihydrochlorid **(Formel I, R und R^1 = H, W = 4-Methylpiperidin-1-yl, Di-HCl-Salz):**

11[4S-(4alpha12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(propylamino)acetyl]amino]-2-naphthacencarboxamid Dihydrochlorid **(Formel I, R und R^1 = H, W = Propylamino, Di-HCl-Salz) ;**

[4S-(4alpha,12aalpha)]-9-[[(Butylamino)acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid Dihydrochlorid **(Formel I, R und R^1 = H, W = n-Butylamino, Di-HCl-Salz) ;**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[2-(dimethylamino)-1-oxopropyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10, 12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid Dihydrochlorid **(Formel I, R =CH_3, R^1 = H, W = Dimethylamino, Di-HCl-Salz);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-11,1-dioxo-9-[[(pentylamino)acetyl]amino]-2-naphthacencarboxamid Monohydrochlorid **(Formel I, R und R^1 = H, W = Pentylamino, Di-HCl-Salz) ;**

[7S-(7alpha,10aalpha)]-N-9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-1-piperidinacetamid Dihydrochlorid **(Formel I, R und R^1 = H, W = Piperidino, Di-HCl-Salz);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(phenylmethyl)amino]acetyl]amino]-2-naphthacencarboxamid Dihydrochlorid **(Formel I, R und R^1 = H, W = Benzylamino, Di-HCl-Salz);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(2-thienylmethyl)amino]acetyl]amino]-2-naphthacencarboxamid Dihydrochlorid **(Formel I, R und R^1 = H, W = Thien-2-ylmethylamino, Di-HCl-Salz);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(2-methylpropyl)-amino]acetyl]amino]-1,11-dioxo-2-naphthacencarboxamid Dihydrochlorid **(Formel I, R und R^1 = H, W = Isobutylamino, Di-HCl-Salz);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(2-pyridinylmethyl]amino]acetyl]amino]-2-naphthacencarboxamid Dihydrochlorid **(Formel I, R und R^1 = H, W = Pyridin-2-ylmethylamino, Di-HCl-Salz);**

[4S-(4alpha,12aalpha)]-9-[[(Diethylamino)acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid Dihydrochlorid **(Formel I, R und R^1 = H, W = Diethylamino, Di-HCl-Salz) ;**

[7S-(7alpha, 10aalpha)]-N-9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-alpha-methyl-1-pyrrolidincarboxamid **(Formel I, R =CH_3, R^1 = H, W = Pyrrolidin-1-yl);**

[4S-(4alpha,12aalpha)]-9-[[[(Cyclopropylmethyl)amino]-acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid Dihydrochlorid **(Formel I, R und R^1 = H, W = Cyclopropylmethylamino, Di-HCl-Salz) ;**

[4S-(4alpha12aalpha)]-4-(Dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamidsulfat, Dihydrochlorid, Monohydrochlorid oder freie Base **(Formel I, R und R^1 = H, W = Dimethylamino);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-N-(1-pyrrolidinyl-methyl)-2-naphthacencarboxamid **(Formel II, R und R^1= H, W = NMe_2 und NR^2R^3 = Pyrrolidino);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[(methoxyamino)-acetyl]amino]-1,11-dioxo-2-naphthacencarboxamid **(Formel 1, R und R^1 = H, W = Methoxyamino) ;**

[4S-(4alpha, 12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11- dioxo-9-[[[(phenylmethoxy)amino]acetyl]amino]-2-naphthacencarboxamid **(Formel I, R und R^1 = H, W = Benzyloxyamino);**

[4S-(4alpha,12aalpha)]-9-[[(Cyclobutylmethylamino)-acetyl]-amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10, 12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid **(Formel I, R und R^1 = H, W = Cyclobutylmethylamino);**

[4S-(4alpha.12aalpha)]-9-[[(2-Butenylamino)acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid **(Formel I, R und R^1 = H, W = 2-Butenylamino);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[(hydroxyamino)-acetyl]amino]-11,1-dioxo-2-naphthacencarboxamid **(Formel I, R und R^1 = H, W = Hydroxyamino);**

[7S-(7alpha, 10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-5-methyl-2,5-diazabicyclo[2.2.1]-heptan-2-acetamid **(Formel I, R und R^1 = H, W = 5-Methyl-2,5-diazabicyclo[2.2.1]hept-2-yl);**

[7S-(7alpha10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-3-methyl-4-morpholinacetamid **(Formel I, R und R1 = H, W = 3-Methyl-4-morpholinyl);**

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-2-azabicyclo[2.2.1]heptan-2-acetamid **(Formel I, R und R^1 = H, W = 2-azabicyclo[2.2.1]hept-2-yl);**

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-hydroxy-1-piperazinacetamid **(Formel I, R und R^1 = H, W = 4-Hydroxypiperazin-1-yl)) ;**

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-3-cyclopropyltetrahydro-4H-thiazin-4-acetamid **(Formel I, R und R^1 = H, W = 3-Cyclopropyl-tetrahydro-4H-thiazin-4-yl));**

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-3-ethyl-lH-pyrrol-1-acetamid **(Formel I, R und R^1 = H, W = 3-Ethyl-1H-pyrrol-1-yl)) ;**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[(1H-imidazol-2-yl-methylamino)acetyl]amino]-1,11-dioxo-2-naphthacencarboxamid **(Formel I, R und R1 = H, W = 1H-Imidazol-2-ylmethylamino);**

[7S-(7alpha, 10aalpha)]-N-[2-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-2-oxoethyl]alanin **(Formel I, R und R^1 = H, W = l-Carboxyethylamino);**

[7S-(7alpha,10aalpha)]-N-[2-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-2-oxoethyl]-carbaminsäure 1,1-Dimethylethylester **(Formel I, R und R^1 = H, W = 1,1-Dimethylethoxycarbonylamino);**

[4S-(4alpha,12aalpha)]-9-[[[(Bicyclo[2.2.2]oct-2-yloxy)-amino]acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacen-carboxamid **(Formel I, R und R^1 = H, W = Bicyclo[2.2.2]oct-2-yloxyamino);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(3-methyl-2-butenyl)amino]acetyl]amino]-1,11-dioxo-2-naphthacencarboxamid **(Formel I, R und R^1 = H, W = 3-Methyl-2-butenylamino);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[4-[(2-methyl-1-oxopropyl) amino]phenyl]amino]acetyl]amino]-1,11-dioxo-2-naphthacencarboxamid **(Formel I, R und R^1 = H, W = 4-[(2-Methyl-1-oxopropyl)amino]phenylamino) ;**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[2-[[(1-methyl-1H-imidazol-2-yl)methyl]amino]-1-oxopropyl]amino]-1,11-dioxo-2-naphthacencarboxamid **(Formel I, R = CH_3, R^1 = H, W = 1-Methyl-1H-Imidazol-2-yl)methylamino) ;**

[4S-(4alpha,12aalpha)]-9-[[2-(Dicyclopropylamino)-1-oxopropyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,-11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacen-carboxamid **(Formel I, R = CH_3, R^1 = H, W = Dicyclopropylamino);**

[7S-(7alpha, 10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-methoxy-a-methyl-1-piperazincarboxamid **(Formel I, R = CH_3, R^1 = H, W = 4-Methoxypiperazin-1-yl);**

[7S-(7alpha, 10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-tetrahydro-a,2-dimethyl-4H-1,4-thiazin-4-acetamid **(Formel I, R = CH_3, R^1 = H , W = Tetrahydro-2-methyl-4H-1,4-thiazin-4-yl);**

[7S-(7alpha, 10aalpha)]-[2-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-2-oxo-1-methylethyl]carbaminsäure 2-Propenylester **(Formel I, R = CH_3, R^1 = H, W = 2-Propenyloxycarbonylamino);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[2-[[3-(methylsulfonyl)phenyl]amino]-1-oxopropyl]amino]-1,11-dioxo-2-naphthacencarboxamid **(Formel I, R = CH_3, R^1 = H, W = 3-(Methylsulfonyl)phenylamino) ;**

[4S-(4alpha, 12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-9-[

[2-methy]-2-(methylamino)-1-oxopropyl]amino]-1,1-dioxo-2-naphthacencarboxamid **(Formel I, R und R^1 = Me, W = Methylamino);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[2-(dimethylamino)-2-methyl-1-oxopropyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid **(Formel I, R und R^1 = Me, W = Dimethylamino);**

[4S-(4alpha,12aalpha)]-9-[[2-[(1,1-dimethylethyl)methylamino]-1-oxobutyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid **(Formel I, R = Et, R^1 = H, W = N-methyl-t-butylamino);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[2-(dimethylamino)-3,3-dimethyl-1-oxobutyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacen-carboxamid **(Formel I, R = ^{t}Bu, R^1 = H, W = Dimethylamino);**

[4S-(4alpha, 12aalpha)]-4-(Dimethylamino)-9-[[2-(ethylamino)-2-methyl-1-oxobutyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid **(Formel I, R = Et, R^1 = Me, W = Ethylamino);**

[4S- (4alpha,12aalpha)]-4-(Dimethylamino)-9-[[2-(dimethylamino)-3-hydroxy-1-oxopropyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid **(Formel I, R = CH_2OH, R^1 = H, W = Dimethylamino);**

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-a-(hydroxymethyl)-4-methyl-1H-imidazol-1-acetamid **(Formel I, R = CH_2OH, R^1 = H, W = 4-Methyl-1H-imidazol-1-yl);**

[4S-(4alpha, 12aalpha)]-9-[[2-(Diethylamino)-3-mercapto-1-oxopropyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid **(Formel I, R = Mercaptomethyl, R^1 = H, W = Dimethylamino);**

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-α-(mercaptomethyl)-1-piperazin-acetamid **(Formel I, R = Mercaptomethyl, R^1 = H, W = Piperazin-1-yl)** ;

[7S-(7alpha,10aalpha]-4-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-3-(hexylamino)-4-oxobutansäure **(Formel I, R = Carboxymethyl, R^1 = H, W = Hexylamino);**

[7S-(7alpha,10aalpha)]-5-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-4-(cyclopropylamino)-5-oxopentansäure **(Formel I, R = 2-Carboxylethyl, R^1 = H, W = Cyclopropylamino);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[2-(dimethylamino)-2-phenylacetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid **(Formel I, R = Phenyl, R^1 = H, W = Dimethylamino);**

[4S-(4alpha,12aalpha)]-9-[[(Butylamino)(4-hydroxy-phenyl)acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid **(Formel I, R = 4-Hydroxyphenyl, R^1 = H, W = Butylamino);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[2-(dimethylamino)-2-(4-methoxyphenyl)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid **(Formel I, R = 4-Methotyphenyl, R^1 = H, W = Dimethylamino);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[2-(ethylmethylamino)-2-[4-(trifluormethyl)phenyl]acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid **(Formel I, R = 4-Trifluoromethylphenyl, R^1 = H, W = N-Ethylmethylamino);** oder

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[[4-(dimethylamino)phenyl](2-propenylamino)acetyl]amino]-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid **(Formel I, R = 4-(Dimethylamino)phenyl, R^1 = H, W = 2-Propenylamino).**

7. Eine Verbindung, welche eine der folgenden ist:

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a-,6,6a,7,10,10a,12-octahydro-1-8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-ethyl-lH-pyrazol-1-acetamid, **(Formel I, R und R^1 = H, W = 4-Ethyl-1H-pyrazol-1-yl);**

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[methyl-(phenylmethyl)amino]acetyl]amino]-2-naphthacencarboxamid, **(Formel I, R und R^1 = H, W = N-Methylbenzylamino);**

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-6-methyl-2-azabicyclo[2,2,2]octan-2-acetamid. **(Formel I, R**

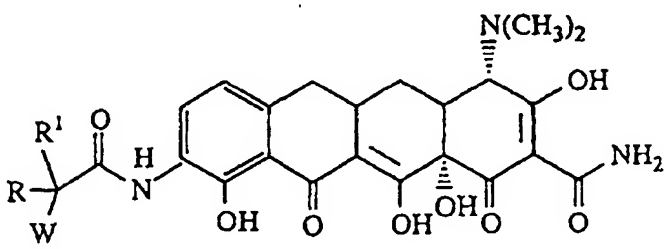
und R^1 = H, W = 6-Methyl-2-azabicyclo-[2.2.2]octan-2-yl);
[4S-(4alpha, 12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[[(2-methylcyclopropyl)oxy]amino]acetyl]amino]-1,11-dioxo-2-naphthacencarboxamid **(Formel I, R und R^1 = H, W = (2-Methylcyclopropyl)-oxyamino);**
[7S-(7alpha, 10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-3-ethyl-1-pyrrolidinacetamid. **(Formel I, R und R^1 = H, W = 3-Ethylpyrrolidin-1-yl);**
[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy10,12-dioxo-2-naphthacenyl]-4-(aminomethyl)-a-methyl-1-piperidinacetamid, **(Formel I, R = CH_3, R^1 = H, W = 4-Aminomethylpiperidin-1-yl) ;**
[4S-(4alpha, 12aalpna)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[2-[[(3-methylcyclobutyl)oxy]amino]-1-oxobutyl]amino]-1,11-dioxo-2-naphthacencarboxamid Hydrobromid, **(Formel I, R = H, R^1 = Et, W = 3-Methylcyclobutyloxyamino);**
[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy10,12-dioxo-2-naphthacenyl]-a-ethyl-4-methyl-2-isoxazolidinacetamid; **(Formel I, R = Et, R^1 = H, W = 4-Methyl-isoxazolidin-2-yl) ;**
[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-a-ethyl-3-methyl-4H-1,2,4-triazol-4-acetamid, **(Formel I, R = Et, R^1 = H, W = 3-Methyl-4H-1,2,4-triazol-4-yl) ;**
oder
[7S-(7alpha,10aalpha)]-4-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-3-[ethyl(phenylmethyl)amino]-4-oxobutansäure **(Formel I, R = Carboxymethyl, R^1 = H, W = N-Ethylbenzylamino).**

8. Verbindung gemäss Anspruch 3, welche eine der folgenden ist:

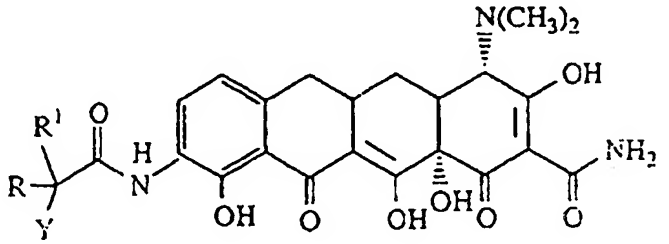
[4S-(4α, 12aα)]-9-[(Bromacetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid Monohydrochlorid **(Formel III, R und R^1 = H, Y steht für Br, HCl-Salz) ;**
[4S-(4α, 12aα)]-9-[(Chloracetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid Monohydrochlorid **(Formel III, R und R^1 = H, Y steht für Cl, HCl-Salz) ;**
[4S-(4α, 12aα)]-9-[(Bromacetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid Monohydrobromid **(Formel III, R und R^1 = H, Y steht für Br, HBr-Salz) ;**
[4S-(4α, 12aα)]-9-[(Bromacetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid Monosulfat **(Formel III, R und R^1 = H, Y steht für Br, Monosulfatsalz) ;**
[4S-(4α,12aα)]-9-[(2-Brom-1-oxopropyl)amino]-4-(dimethyl-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy1,11-dioxo-2-naphthacencarboxamid Monohydrobromid **(Formel III, R = CH_3, R^1 = H, Y steht für Cl, HBr-Salz);**
[4S-(4α, 12aa)]-9-[(2-Brom-2-methyl-1-oxopropyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid Hydrobromid **(Formel III, R und R^1 = CH_3, Y = Br) ;**
[4S-(4α,12aα)]-9-[(2-Brom-1-oxobuty])amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10-12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid Hydrobromid **(Formel III, R = Et, R^1 = H, Y = Br) ;**
[4S-(4α,12aα)]-9-[(2-Brom-1-oxopentyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid Hydrobromid **(Formel III R = Pr, R^1 = H, Y = Br) ;**
[4S-(4α-,12aα)]-9-[(2-Brom-2-methyl-1-oxobutyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid Hydrobromid **(Formel III, R = Et, R^1 = Me, Y = Br) ;**
[4S-(4α,12aα)]-9-[(2-Brom-3-hydroxy-1-oxopropyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid Hydrobromid **(Formel III, R = Et, R^1 = Me, Y = Br);**
[4S- (4α, 12aα)]-9-[(2-Brom-3-mercapto-1-oxopropyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid Hydrobromid **(Formel III, R = Mercap-**

tomethyl, R^1 = H, Y = Br);
[7S-(7α,10aα)]-4-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-3-brom-4-oxobutansäure Hydrobromid **(Formel III, R = Carboxymethyl, R^1 = H, Y = Br,);**
[7S-(7α,10aα)]-5-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-4-brom-5-oxopentansäure Hydrobromid **(Formel III, R = 2-Carboxyethyl, R^1 = H, Y = Br,);**
[4S-(4α, 12aα)]-9-[(Bromphenylacetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid Hydrobromid **(Formel III, R = Phenyl, R^1 = H, Y = Br) ;**
[4S-(4α, 12aα)]-9-[[Brom(4-hydroxyphenyl)-ecetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid Hydrobromid **(Formel III, R = 4-Hydroxyphenyl, R^1 = H, Y = Br);**
[4S-(4α,12aα)]-9-[[Brom(4-methoxyphenyl)acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid Hydrobromid, **(Formel III, R = 4-Methoxyphenyl, R^1 = H, Y = Br) ;**
[4S-(4a,12aa)]-9-[[Brom[4-(trifluormethyl)phenyl]acetyl]-amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid Hydrobromid **(Formel III, R = 4-Trifluormethylphenyl, R^1 = H, Y = Br) ;** und
[4S-(4α,12aα)]-9-[[Brom[4-(dimethylamino)phenyl]acetyl]-amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid Hydrobromid **(Formel III, R = 4-(Dimethylamino)phenyl, R^1 = H, Y = Br) .**

9. Verfahren zum Herstellen einer Verbindung, oder ihres organischen und anorganischen Salzes oder Metallkomplexes der Formel:

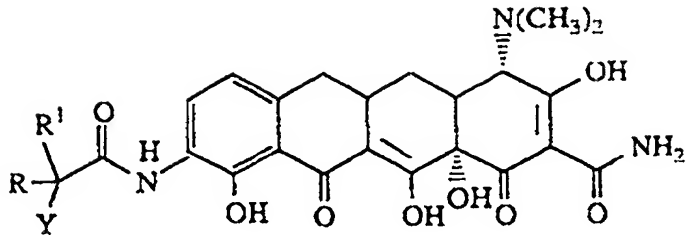


gemäss Anspruch 1, welches umfasst: Umsetzen eines 9[(Halogenacyl)amido]-6-demethyl-6-deoxytetracyclins, oder seines organischen und anorganischen Salzes oder Metallkomplexes der Formel:

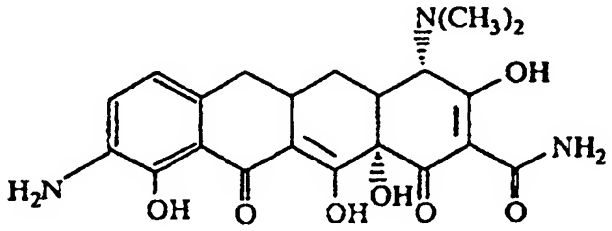


gemäss Anspruch 3 mit einem Nucleophil der Formel WH, worin W wie in Anspruch 1 definiert ist, in einem polaraprotischen Lösungsmittel und in einer inerten Atmosphäre.

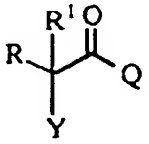
10. Verfahren zum Herstellen einer Verbindung oder ihres organischen und anorganischen Salzes oder Metallkomplexes der Formel:



gemäss Anspruch 3, welches umfasst: Umsetzen von 9-Amino-6-demethyl-6-deoxytetracyclin oder seines organischen und anorganischen Salzes oder Metallkomplexes der Formel:

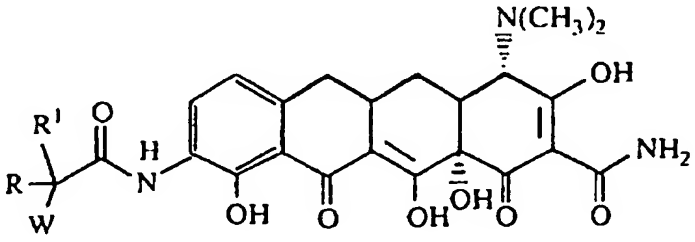


mit einem graden oder verzweigten Halogenacylhalogenid der Formel:

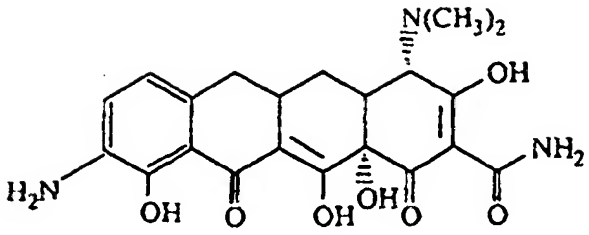


worin Y, R und R^1 wie in Anspruch 3 definiert sind und Q Halogen darstellt, ausgewählt aus Brom, Chlor, Iod und Fluor, in einem inerten Lösungsmittel in einem polar-aprotischen Lösungsmittel und in Gegenwart einer Base.

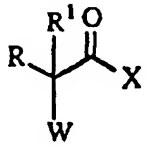
11. Verfahren zum Herstellen einer Verbindung oder ihres organischen und anorganischen Salzes oder Metallkomplexes der Formel:



gemäss Anspruch 1, welches umfasst: Umsetzen eines 9-Amino-6-deoxytetracyclins oder seines organischen oder anorganischen Salzes oder Metallkomplexes der Formel:



mit einem Säurehalogenid der Formel:



worin R, R^1 und W wie in Anspruch 1 definiert sind, und X ausgewählt wird aus Brom, Chlor, Iod und Fluor, in einem inerten Lösungsmittel in einem polar-aprotischen Lösungsmittel und in Gegenwart einer Base.

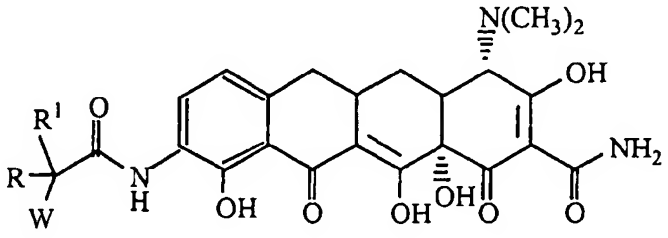
12. Verwendung einer Verbindung wie in einem der Ansprüche 1, 2, 5, 6 oder 7 beansprucht, bei der Herstellung einer Arznei zur Verhinderung, Behandlung oder Bekämpfung bakterieller Infektionen in Warmblütern.

13. Pharmazeutische Substanz-Zusammensetzung, umfassend eine pharmakologisch wirksame Menge einer Verbindung gemäss Anspruch 1, 2, 5, 6 oder 7 in Verbindung mit einem pharmazeutisch annehmbaren Träger.

14. Tierärztliche Zusammensetzung, welche eine pharmakologisch wirksame Menge einer Verbindung von Anspruch 1, 2, 5, 6 oder 7 und einem pharmazeutisch annehmbaren Träger umfasst.

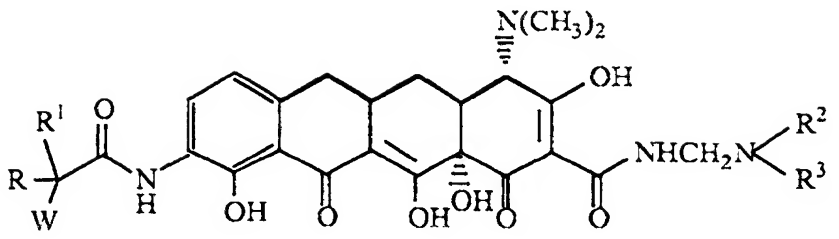
Revendications

1. Composé de formule :



(I)

ou



(II)

dans laquelle :

R est choisi parmi

hydrogène;
groupement (C_1-C_8)alkyle en chaîne droite ou ramifiée choisi parmi méthyle, éthyle, propyle, isopropyle, butyle, isobutyle, pentyle, hexyle, heptyle et octyle;
groupement α-mercapto(C_1-C_4)alkyle choisi parmi mercaptométhyle, α-mercaptoéthyle, α-mercapto-1-méthyléthyle, α-mercaptopropyle et α-mercaptobutyle;
groupement α-hydroxy (C_1-C_4)alkyle choisi parmi hydroxyméthyle, α-hydroxyéthyle, α-hydroxy-1-méthyléthyle, α-hydroxypropyle et α-hydroxybutyle;
groupement carboxyl(C_1-C_8)alkyle;
groupement (C_6-C_{10})aryle choisi parmi phényle, α-naphtyle et β-naphtyle; ou groupement (C_6-C_{10})aryle substitué (substitution choisie parmi hydroxy, halogène, (C_1-C_4)alkoxy, trihalo(C_1-C_3)alkyle, nitro, amino, cyano, (C_1-C_4)alkoxycarbonyle, (C_1-C_3)alkylamino et carboxy);
groupement (C_7-C_9)aralkyle choisi parmi benzyle, 1-phényléthyle, 2-phényléthyle et phénylpropyle; ou groupement (C_7-C_9)aralkyle substitué [substitution choisie parmi halo, (C_1-C_4)alkyle, nitro, hydroxy, amino, (C_1-C_4)alkylamino mono- ou disubstitué, (C_1-C_4)alkoxy, (C_1-C_4)alkylsulfonyle, cyano et carboxy];

R^1 est choisi parmi hydrogène et (C_1-C_6)alkyle choisi parmi méthyle, éthyle, propyle, isopropyle, butyle, isobutyle, pentyle et hexyle; quand R n'est pas égal à R^1 la stéréochimie du carbone asymétrique (c'est-à-dire le carbone portant le substituant W) peut être soit le racémate (DL) ou les énantiomères individuels (L ou D);

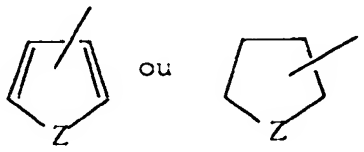
W est choisi parmi

amino;
hydroxylamino;
groupement amino monosubstitué par un groupement (C_1-C_{12})alkyle en chaîne droite ou ramifiée, substitution choisie parmi méthyle, éthyle, n-propyle, 1-méthyléthyle, n-butyle, 1-méthylpropyle, 2-méthylpropyle, 1,1-diméthyléthyle, n-pentyle, 2-méthylbutyle, 1,1-di-méthylpropyle, 2,2-diméthylpropyle, 3-méthylbutyle, n-hexyle, 1-méthylpentyle, 1,1-diméthylbutyle, 2,2-diméthylbutyle, 3-méthylpentyle, 1,2-diméthylbutyle, 1,3-diméthylbutyle, 1-méthyl-1-éthylpropyle, heptyle, octyle, nonyle, décyle, undécyle et dodécyle et les diastéréomères et énantiomères dudit groupement amino monosubstitué par un alkyle en chaîne droite ou ramifiée;
groupement amino monosubstitué par (C_3-C_8)cycloalkyle, substitution choisie parmi cyclopropyle, trans-1,2-diméthylcyclopropyle, cis-1,2-diméthyl-cyclopropyle, cyclobutyle, cyclopentyle, cyclohexyle, cycloheptyle, cyclooctyle, bicyclo[2.2.1]hept-2-yle et bicyclo[2.2.2]oct-2-yle et les diastéréomères et énantiomères dudit groupement amino monosubstitué par (C_3-C_8)cycloalkyle ;
groupement amino monosubstitué par [(C_4-C_{10}) cycloalkyl]alkyle, substitution choisie parmi (cyclopropyl) méthyle, (cyclopropyl)éthyle, (cyclobutyl)méthyle, (trans-2-méthylcyclopropyl)méthyle et (cis-2-méthylcyclobutyl)-méthyle;
groupement amino monosubstitué par (C_3-C_{10})alcényle, substitution choisie parmi allyle, 3-butényle, 2-butényle (cis ou trans), 2-pentényle, 4-octényle, 2,3-diméthyl-2-butényle, 3-méthyl-2-butényle, 2-cyclopentényle et 2-cyclohexényle;
groupement amino monosubstitué par (C_6-C_{10})aryle, substitution choisie parmi phényle et naphtyle;
groupement (C_7-C_{10})aralkylamino, substitution choisie parmi benzyle, 2-phényléthyle, 1-phényléthyle, 2-

(naphtyl)méthyle, 1-(naphtyl)méthyle et phénylpropyle:
groupement amino monosubstitué par (C_6-C_{10})aryle substitué [substitution choisie parmi (C_1-C_5)acyle, (C_1-C_5)acylamino, (C_1-C_4)alkyle, (C_1-C_8)alkylamino mono ou disubstitué, (C_1-C_4)alkoxy, (C_1-C_4)alkoxycarbonyle, (C_1-C_4)alkylsulfonyle, amino, carboxy, cyano, halogène, hydroxy, nitro et trihalo(C_1-C_3)-alkyle] ;
groupement (C_2-C_{14})alkylamino disubstitué en chaîne droite ou ramifiée symétrique, substitution choisie parmi diméthyle, diéthyle, diisopropyle, di-n-propyle, di-n-butyle et diisobutyle;
groupement (C_3-C_{14})cycloalkylamino disubstitué symétrique, substitution choisie parmi dicyclopropyle, dicyclobutyle, dicyclopentyle, dicyclohexyle et dicycloheptyle;
groupement (C_3-C_{14})alkylamino disubstitué en chaîne droite ou ramifiée asymétrique dans lequel le nombre total de carbones dans la substitution n'est pas de plus de 14;
groupement (C_4-C_{14})cycloalkylamino disubstitué asymétrique dans lequel le nombre total de carbones dans la substitution n'est pas de plus de 14;
groupement (C_2-C_8)azacycloalkyle ou (C_2-C_8)azacycloalkyle substitué choisi parmi aziridinyle, azétidinyle, pyrrolidinyle, pipéridinyle, 4-méthylpipéridinyle, 2-méthylpyrrolidinyle, cis-3,4-diméthylpyrrolidinyle, trans-3,4-diméthylpyrrolidinyle, 2-azabicyclo[2.1.1]hex-2-yle, 5-azabicyclo[2.1.1]hex-5-yle, 2-azabicyclo-[2.2.1]hept-2-yle, 7-azabicyclo[2.2.1]-hept-7-yle et 2-azabicyclo[2.2.2]oct-2-yle et les diastéréomères et énantiomères dudit groupement (C_2-C_8)azacycloalkyle et (C_2-C_8)azacycloalkyle substitué;
groupement 1-azaoxacycloalkyle choisi parmi morpholinyle et 1-aza-5-oxacycloheptane; groupement 1-azaoxacycloalkyle substitué choisi parmi 2-(C_1-C_3)alkylmorpholinyle, 3-(C_1-C_3)alkylisoxazolidinyle, tétrahydrooxazinyle et 3,4-dihydrooxazinyle;
groupement [1,n]-diazacycloalkyle et [1,n]diazacycloalkyle substitué choisi parmi pipérazinyle, 2-(C_1-C_3) alkylpipérazinyle, 4-(C_1-C_3)alkylpipérazinyle, 2,4-diméthylpipérazinyle, 4-(C_1-C_4)alkoxypipérazinyle, 4-(C_6-C_{10})aryloxypipérazinyle, 4-hydroxypipérazinyle, 2,5-diazabicyclo-[2.2.1]hept-2-yle, 2,5-diaza-5-méthylbicyclo-[2.2.1]hept-2-yle, 2,3-diaza-3-méthylbicyclo-[2.2.2]oct-2-yle et 2,5-diaza-5,7-diméthylbicyclo [2.2.2]-oct-2-yle et les diastéréomères ou énantiomères dudit groupement [1,n]-diazacycloalkyle et [1,n]-diazacycloalkyle substitué;
groupement 1-azathiacycloalkyle et 1-azathiacycloalkyle substitué choisi parmi thiomorpholinyle, 2-(C_1-C_3) alkythiomorpholinyle et 3-(C_3-C_6) cycloalkylthiomorpholinyle;
groupement N-azolyle et N-azolyle substitué choisi parmi 1-imidazolyle, 2-(C_1-C_3) alkyl-1-imidazolyle, 3-(C_1-C_3)alkyl-1-imidazolyle, 1-pyrrolyle, 2-(C_1-C_3)alkyl-1-pyrrolyle, 3-(C_1-C_3)alkyl-1-pyrrolyle, 1-pyrazolyle, 3-(C_1-C_3)alkyl-l-pyrazolyle, indolyle, 1-(1,2,3-triazolyle), 4-(C_1-C_3)alkyl-1-(1,2,3-triazolyle), 5-(C_1-C_3) alkyl-1-(1,2,3-triazolyle), 4-(1,2,4-triazolyle), 1-tétrazolyle, 2-tétrazolyle et benzimidazolyle;
groupement (hétérocycle)amino choisi parmi 2- ou 3-furanylamino, 2- ou 3-thiénylamino, 2-, 3-ou 4-pyridylamino, 2- ou 5-pyridazinylamino, 2-pyrazinylamino, 2-(imidazolyl)amino, (benzimidazolyl)amino et (benzothiazolyl)-amino et groupement (hétérocycle)amino substitué comme défini ci-dessus avec la substitution choisie parmi (C_1-C_6)alkyle en chaîne droite ou ramifiée;
groupement (hétérocycle)méthylamino choisi parmi 2-ou 3-furylméthylamino, 2- ou 3-thiénylméthylamino, 2-, 3- ou 4-pyridylméthylamino, 2- ou 5-pyridazinylméthylamino, 2-pyrazinylméthylamino, 2-(imidazolyl) méthylamino, (benzimidazolyl)méthylamino et (benzothiazolyl)-méthylamino et groupement (hétérocycle)-méthylamino substitué comme défini ci-dessus avec substitution choisie parmi (C_1-C_6)alkyle en chaîne droite ou ramifiée;
groupement carboxy(C_2-C_4)alkylamino choisi parmi acide aminoacétique, acide α-aminopropionique, acide β-aminopropionique, acide α-amino-butyrique et acide β-aminobutyrique et les énantiomères dudit groupement carboxy(C_2-C_4)alkylamino;
groupement (C_1-C_4)alkoxycarbonylamino, substitution choisie parmi méthoxycarbonyle, éthoxycarbonyle, allyloxycarbonyle, propoxycarbonyle, isoproproxycarbonyle, 1,1-diméthyléthoxycarbonyle, n-butoxycarbonyle et 2-méthylpropoxycarbonyle;
groupement (C_1-C_4)alkoxyamino, substitution choisie parmi méthoxy, éthoxy, n-propoxy, 1-méthyléthoxy, n-butoxy, 2-méthylpropoxy, et 1,1-diméthyléthoxy;
groupement (C_3-C_8)cycloalkoxyamino, substitution choisie parmi cyclopropoxy, trans-1,2-diméthylcyclopropoxy, cis-1,2-diméthylcyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, cycloheptoxy, cyclooctoxy, bicyclo[2.2.1]hept-2-yloxy et bicyclo[2.2.2]-oct-2-yloxy et les diastéréomères et énantiomères dudit groupement (C_3-C_8)cycloalkoxyamino;
groupement (C_6-C_{10})aryloxyamino choisi parmi phénoxyamino, 1-naphtyloxyamino et 2-naphtyloxyamino; et
groupement (C_7-C_{11})arylalkoxyamino substitution choisie parmi benzyloxy, 2-phényléthoxy, 1-phényléthoxy, 2-(naphtyl)méthoxy, 1-(naphtyl)méthoxy et phénylpropoxy:

R^2 et R^3 sont indépendamment choisis parmi

(i) hydrogène, à condition que R^2 et R^3 ne soient pas ensemble hydrogène;
(ii) groupement (C_1-C_3)alkyle en chaîne droite ou ramifiée choisie parmi méthyle, éthyle, n-propyle ou 1-méthyléthyle:
(iii) groupement (C_6-C_{10})aryle choisi parmi phényle, α-naphtyle ou β-naphtyle;
(iv) groupement (C_7-C_9)aralkyle:
(v) un groupement hétérocycle choisi parmi un cycle aromatique à cinq membres ou un cycle saturé avec un hétéroatome N, O, S ou Se ayant facultativement un cycle benzo ou pyrido fusionné dessus :

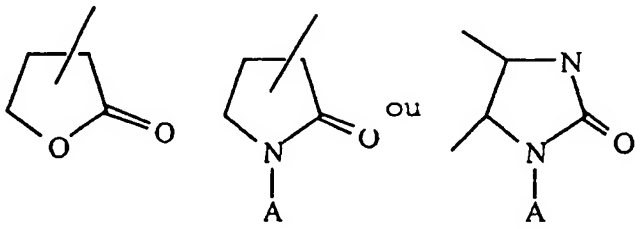


Z = N, O, S ou Se

(vi) un cycle aromatique à cinq membres avec deux hétéroatomes N, O, S ou Se ayant facultativement un cycle benzo ou pyrido fusionné dessus:

Z or Z^1 = N, O, S ou Se

(vii) un cycle saturé à cinq membres avec un ou deux hétéroatomes N, O, S ou Se et un hétéroatome adjacent attenant O :



(dans lequel A est choisi parmi hydrogène; (C_1-C_4)alkyle en chaîne droite ou ramifiée; C_6-aryle; C_6-aryle substitué (substitution choisie parmi halo, (C_1-C_4) alkoxy, trihalo(C_1-C_3)alkyle, nitro, amino, cyano, (C_1-C_4)alkoxycarbonyle, (C_1-C_3)-alkylamino ou carboxy); benzyle, 1-phényléthyle, 2-phényléthyl ou phénylpropyle);
(viii) un cycle aromatique à six membres avec un à trois hétéroatomes N,
(ix) un cycle saturé à six membres avec un ou deux hétéroatomes N, O, S ou Se et un hétéroatome adjacent attenant O ;
(x) -$(CH_2)_nCOOR^4$ où n=0-4 et R^4 est choisi parmi hydrogène; groupement (C_1-C_3)alkyle en chaîne droite ou ramifiée choisi parmi méthyle, éthyle, n-propyle ou 1-méthyléthyle;
ou
(xi) groupement (C_6-C_{10})aryle choisi parmi phényle, α-naphtyle, ou β-naphtyle;

ou **R^2 et R^3** pris conjointement sont

(i) $-(CH_2)_2B(CH_2)_2-$, où B est choisi parmi $(CH_2)_n$ et n=0-1, -NH, $-N(C_1-C_3)$alkyle [en chaîne droite ou ramifiée], $-N(C_1-C_4)$alkoxy, oxygène, soufre;
ou
(ii) congénères substitués choisis parmi (L ou D)proline et éthyl(L ou D)prolinate.

et les sels pharmacologiquement acceptables organiques et inorganiques ou complexes métalliques.

2. Composé selon la revendication 1, dans lequel :

R et **R^1** sont indépendamment choisis parmi hydrogène, méthyle ou éthyle, et quand R n'est pas égal à R^1 la stéréochimie du carbone asymétrique peut être soit le racémate (DL) ou les énantiomères individuels (L ou D) ;

w est choisi parmi amino, méthylamino, éthylamino, n-propylamino, 1-méthyléthylamino, n-butylamino, 1-méthylpropylamino, 2-méthylpropylamino, n-hexylamino, n-octylamino, cyclopropylamino, cyclopentylamino, cyclohexylamino, (cyclopropyl) méthylamino, (cyclopropyl)éthylamino, allylamino, 3-buténylamino, benzylamino, 2-phényléthylamino, 1-phényléthylamino, diméthylamino, diéthylamino, méthyl(éthyl)amino; pyrrolidinyle, pipéridinyle, morpholinyle, 2-(C_1-C_3)alkylmorpholinyle, pipérazinyle, 2-(C_1-C_3)-alkyl-pipérazinyle, 4-(C_1-C_3) alkylpipérazinyle, 2,5-diaza-5-méthylbicyclo[2.2.1]hept-2-yle, (et les diastéréomères ou énantiomères dudit groupement [1,n] -diazacycloalkyle et [1,n] -diazacycloalkyle substitué); thiomorpholinyle, 2-(C_1-C_3)alkylthiomorpholinyle, 1-imidazolyle, 2- or 3-thiénylméthylamino, 2-, 3- ou 4-pyridylméthylamino, méthoxycarbonylamino, éthoxycarbonylamino et 1,1-diméthyléthoxycarbonylamino,

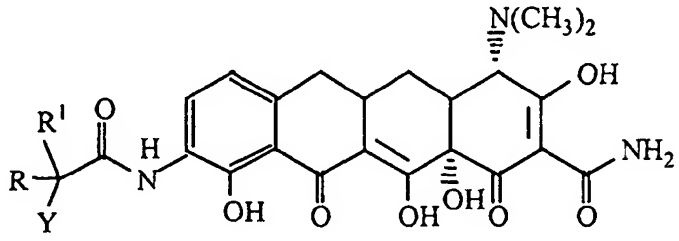
R^2 et **R^3** sont indépendamment choisis parmi hydrogène, méthyle, éthyle, n-propyle et 1-méthyléthyle; avec la condition que R^2 et R^3 ne peuvent pas être ensemble hydrogène;

ou **R^2 et R^3** pris conjointement sont

(i) $-(CH_2)_2B(CH_2)_2-$, où B est choisi parmi $(CH_2)_n$ (où n=0-1), -NH, $-N(C_1-C_3)$alkyle [en chaîne droite ou ramifiée], $-N(C_1-C_4)$alkoxy, oxygène, ou soufre
ou (ii) congénères substitués choisis parmi (L or D)proline et éthyl(L or D)prolinate;

et les sels pharmacologiquement acceptables organiques et inorganiques ou les complexes métalliques.

3. Composé de formule :



(III)

dans laquelle :

Y est choisi parmi brome, chlore, fluor ou iode;
R est choisi parmi hydrogène, méthyle, éthyle, propyle, isopropyle, butyle, isobutyle, pentyle, hexyle, heptyle, octyle, mercaptométhyle, α-mercaptoéthyle, α-mercapto-1-méthyléthyle, α-mercaptopropyle, α-mercaptobutyle, hydroxyméthyle, α-hydroxyéthyle, α-hydroxy-1-méthyléthyle, α-hydroxypropyle, α-hydroxybutyle; un groupement carboxyl(C_1-C_8)alkyle;
un groupement phényle, α-naphtyle ou β-naphtyle chacun facultativement substitué par
hydroxy, halogène, (C_1-C_4)alkoxy, trihalo(C_1-C_3) alkyle, nitro, amino, cyano, (C_1-C_4)alkoxycarbonyle, (C_1-C_3)

alkylamino et carboxy;
ou un groupement benzyle, 1-phényléthyle, 2-phényléthyle ou phénylpropyle chacun facultativement substitué par :
halo, (C_1-C_4)alkyle, nitro, hydroxy, amino, mono- ou di-substitué (C_1-C_4)alkylamino, (C_1-C_4)alkoxy, (C_1-C_4) alkylsulfonyle, cyano et carboxy];
R^1 est choisi parmi hydrogène, méthyle, éthyle, propyle, isopropyle, butyle, isobutyle, pentyle et hexyle; et quand R n'est pas égal à R^1 la stéréochimie du carbone asymétrique (c'est-à-dire le carbone portant le substituant Y) peut être soit le racémate (DL) ou les énantiomères individuels (L ou D); et le sel pharmacologiquement acceptable organique et inorganique ou les complexes métalliques.

4. Composé selon la revendication 3, dans lequel :

Y est choisi parmi brome, chlore, fluor et iode;
R est choisi parmi hydrogène, méthyle ou éthyle,
et
R^1 est choisi parmi hydrogène, méthyle ou éthyle, quand R n'est pas égal à R^1 la stéréochimie du carbone asymétrique (c'est-à-dire le carbone portant le substituant Y) peut être soit le racémate (DL) ou les énantiomères individuels (L ou D); et le sel pharmacologiquement acceptable organique et inorganique ou complexes métalliques.

5. Composé selon la revendication 1 dans lequel lesdits sels comprennent : acides chlorhydrique, bromhydrique, iodihydrique, phosphorique, nitrique, sels de sulfate, acétate, benzoate, citrate, cystéine ou autre acide aminé, fumarate, glycolate, maléate, succinate, tartrate, alkylsulfonate ou arylsulfonate et
lesdits complexes métalliques comprennent : aluminum, calcium, fer, magnésium, manganèse et sels complexes.

6. Composé selon la revendication 1, qui est un des suivants

dichlorhydrate de [4S-(4α, 12aα)]-4-(diméthylamino)-9-[[(hexylamino)acétyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule I, R et R^1 = H, W = n-hexylamino, di HCl sel)** ;

dichlorhydrate de [4S-(4α, 12aα)]-4-(diméthyl)amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-[[(méthylamino)acétyl]amino]-1,11-dioxo-2-naphtacène-carboxamide **(Formule I, R et R^1 = H, W = méthylamino, di HCl sel)** ;

dichlorhydrate de [4S-(4α,12aα)]-4-(diméthylamino)-9-[[(éthylamino)acétyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule I, R et R^1 = H, W = éthylamino, di HCl sel)** ;

dichlorhydrate de [7S-(7a,10aa)]-N-[9-(aminocarbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-1-pyrrolidineacétamide **(Formule I, R et R^1 = H, W = pyrrolidin-1-yle, di HCl sel)** ;

dichlorhydrate de [7S-(7α,10aα)]-N-[9-(aminocarbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-4-méthyl-1-pipéridineacétamide **(Formule I, R et R^1 = H, W = 4-méthylpipéridin-1-yle, di HCl sel)** ;

dichlorhydrate de 11[4S-(4α, 12aα)]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-9-[[(propylamino)acétyl]amino]-2-naphtacène-carboxamide **(Formule I, R et R^1 = H, W = propylamino, di HCl sel)** ;

dichlorhydrate de [4S-(4α,12aα)]-9-[[(butylamino)-acétyl]amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule I, R et R^1 = H, W = n-butylamino, di HCl sel)** ;

dichlorhydrate de [4S-(4α,12aα)]-4-(diméthylamino)-9-[[2-(diméthylamino)-1-oxopropyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10.12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule I, R =CH_3, R^1 = H, W = diméthylamino, di HCl sel)** ;

monochlorhydrate de [4S-(4α,12aα)]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-9-[[(pentylamino)acétyl]amino]-2-naphtacène-carboxamide **(Formule I, R et R^1 = H, W = pentylamino, mono HCl sel)** ;

dichlorhydrate de [7S-(7α,10aα)]-N-9-(aminocarbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-1-pipéridine-acétamide **(Formule I, R et R^1 = H, W = pipéridino, di HCl sel)** ;

dichlorhydrate de [4S-(4α, 12aα)]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-9-[[[(phenylméthyl)amino]acétyl]amino]-2-naphtacènecarboxamide **(Formule I, R et R^1 = H, W = benzylamino, di HCl sel)** ;

dichlorhydrate de [4S-(4α,12aα)]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-9-[[[(2-thiénylméthyl)amino]-acétyl]amino]-2-naphtacènecarboxamide **(Formule I, R et R^1 = H, W = thièn-2-ylméthylamino, di HCl sel)**;

dichlorhydrate de [4S-(4α,12aα)]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-[[[(2-méthylpropyl)amino]-acétyl]amino]-1,11-dioxo-2-naphtacènecarboxamide **(Formule I, R et R^1 = H, W = isobutylamino, di HCl sel)**;

dichlorhydrate de [4S-(4α,12aα)]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-9-[[[(2-pyridinyl-méthyl]amino]acétyl]amino]-2-naphtacènecarboxamide **(Formule I, R et R^1 = H, W = pyridin-2-ylméthylamino, di HCl sel)**;

dichlorhydrate de [4S-(4α,12aα)]-9-[[(diéthylamino)-acétyl]amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule I, R et R^1 = H, W = diéthylamino, di HCl sel)**;

[7S-(7a,10aa)]-N-9-(aminocarbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-α-méthyl-1-pyrrolidine-carboxamide (**Formule I, R =CH_3, R^1 = H, W = pyrrolidin-1-yle)** ;

dichlorhydrate de [4S-(4α,12aα)]-9-[[[(cyclopropyl-méthyl)amino]acétyl]amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule I, R et R^1 = H, W = cyclopropylméthylamino, di HCl sel)** ;

sulfate, dichlorhydrate, monochlorhydrate ou base libre de [4S-(4α, 12aα)]-4-(dimethylamino)-9-[[(diméthylamino)-acétyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacene-carboxamide **(Formule I, R et R^1 = H, W = diméthylamino)**;

[4S-(4α, 12aα)]-4-(diméthylamino)-9-[[(diméthylamino)-acétyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-N-(1-pyrrolidinyl-méthyl)-2-naphtacènecarboxamide **(Formule II, R et R^1 = H, W = NMe_2 et NR^2R^3 = pyrrolidino)**,

[4S-(4α, 12aα)]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-[[(méthoxyamino)-acétyl]amino] -1, 11-dioxo-2-naphtacènecarboxamide **(Formule I, R et R^1 = H, W = méthoxyamino)**;

[4S-(4α,12aα)]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-9-[[[(phénylméthoxy)amino]acétyl]amino]-2-naphtacène-carboxamide **(Formule I, R et R^1 = H, W = benzyloxyamino)**;

[4S-(4α,12aα)]-9-[[(cyclobutylméthylamino)acétyl]-amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène-carboxamide **(Formule I, R et R^1 = H, W = cyclobutylméthylamino)**;

[4S-(4α,12aα)]-9-[[(2-buténylamino)acétyl]amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène-carboxamide **(Formule I, R et R^1 = H, W =2-buténylamino)**;

[4S-(4α,12aα)]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-[[(hydroxyamino)-acétyl]amino]-1,11-dioxo-2-naphtacènecarboxamide **(Formule I, R et R^1 = H, W = hydroxyamino);**

[7S-(7α,10aα)]-N-[9-(aminocarbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-5-méthyl-2,5-diazabicyclo-[2.2.1]heptane-2-acétamide **(Formule I, R et R^1 = H, W = 5-méthyl-2,5-diazabicyclo[2.2.1]hept-2-yle) ;**

[7S-(7a,10aa)]-N-[9-(aminocarbonyl)-7-(diméthyl-amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-3-méthyl-4-morpholine-acétamide **(Formule I, R et R^1 = H, W = 3-méthyl-4-morpholinyle);**

[7S-(7α,10aα)]-N-[9-(aminocarbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-2-azabicyclo[2.2.1]heptane-2-acétamide **(Formule I, R et R^1 = H, W = 2-azabicyclo[2.2.1]hept-2-yle) ;**

[7S-(7α,10aα)]-N-[9-(aminocarbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-4-hydroxy-1-pipérazine-acétamide **(Formule I, R et R^1 = H, W = 4-hydroxypipérazin-1-yle) ;**

[7S-(7α,10aα)]-N-[9-(aminocarbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-3-cyclopropyl-tétrahydro-4H-thiazine-4-acétamide **(Formule I, R et R^1 = H, W = 3-cyclopropyl-tétrahydro-4H-thiazin-4-yle) ;**

[7S-(7α,10aα)]-N-[9-(aminocarbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-3-éthyl-IH-pyrrole-1-acétamide **(Formule I, R et R^1 = H, W = 3-éthyl-1H-pyrrol-1-yle) ;**

[4S-(4α,12aα)]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-[[(1H-imidazol-2-ylméthylamino)acétyl]amino]-1,11-dioxo-2-naphtacène-carboxamide **(Formule I, R et R^1 = H, W = 1H-imidazol-2-ylméthylamino);**

[7S-(7α,10aα)]-N-[2-[[9-(aminocarbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]amino]-2-oxoéthyl]alanine **(Formule I, R et R^1 = H, W = 1-carboxyéthylamino);**

ester 1,1-diméthyléthylique de l'acide [7S-(7α, 10aα)]-N-[2-[[9-(aminocarbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl] amino]-2-oxoéthyl]carbamique **(Formule I, R et R^1 = H, W = 1,1-diméthyléthoxycarbonylamino);**

[4S-(4α,12aα)]-9-[[[(bicyclo[2.2.2]oct-2-yloxy)amino]-acétyl]amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule I, R et R^1 = H, W = bicyclo[2.2.2]oct-2-yloxyamino);**

[4S-(4α,12aα)]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-[[[(3-méthyl-2-butényl)amino]acétyl]amino]-1,11-dioxo-2-naphtacène-carboxamide **(Formule I, R et R^1 = H, W = 3-méthyl-2-buténylamino);**

[4S-(4α,12aα)]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-[[[[4-[(2-méthyl-1-oxopropyl)amino]phenyl]amino]-acetyl]amino]-1,11-dioxo-2-naphtacènecarboxamide **(Formule I, R et R^1 = H, W = 4-[(2-méthyl-1-oxopropyl)amino]phénylamino);**

[4S-(4α,12aα)]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-[[2-[[(1-méthyl-1H-imidazol-2-yl)méthyl]amino]-1-oxopropyl]amino]-1,11-dioxo-2-naphtacènecarboxamide **(Formule I, R = CH_3, R^1 = H, W = 1-méthyl-1H-imidazol-2-yl)méthylamino) ;**

[4S-(4α,12aα)]-9-[[2-(dicyclopropylamino)-1-oxopropyl]-amino]-4-(diméthylamino)-1,4,4a,5,5a,6,-11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène-carboxamide **(Formule I, R = CH_3, R^1 = H, W = dicyclopropylamino) ;**

[7S-(7α,10aα)]-N-[9-(aminocarbonyl)-7-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-10,12-dioxo-2-naphtacényl]-4-méthoxy-α-méthyl-1-pipérazinecarboxamide **(Formule I, R = CH_3, R^1 = H, W = 4-méthoxypipérazin-1-yl)** ;

[7S-(7α,10aα)]-N-[9-(aminocarbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-tétrahydro-α,2-diméthyl-4H-1,4-thiazine-4-acétamide **(Formule I, R = CH_3, R^1= H , W = tétrahydro-2-méthyl-4H-1,4-thiazin-4-yle);**

ester 2-propénylique de l'acide [7S-(7α,10aα)]-[2-[[9-(aminocarbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]amino]-2-oxo-1-méthyléthyl]carbamique **(Formule I, R = CH_3, R^1 = H, W = 2-propényloxy-carbonylamino);**

[4S-(4α, 12aα)]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-[[2-[[3-(méthylsulfonyl)phényl]amino]-1-oxopropyl]amino]-1,11-dioxo-2-naphtacènecarboxamide **(Formule I, R = CH_3, R^1 = H, W = 3-(méthylsulfonyl)phénylamino);**

[4S-(4α,12aα)]-4-(diméthylamino)-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-[[2-méthyl-2-(méthylamino)-1-oxopropyl]amino]-1,1-dioxo-2-naphtacène-carboxamide **(Formule I, R et R^1 = Me, W = méthylamino);**

[4S-(4α,12aα)]-4-(diméthylamino)-9-[[2-(diméthylamino)-2-méthyl-1-oxopropyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule I, R et R^1 = Me, W = diméthylamino);**

[4S-(4α,12aα)]-9-[[2-[(1,1-diméthyléthyl)-méthylamino]-1-oxobutyl]amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule I, R = Et, R^1 = H, W = N-méthyl-t-butylamino)** ;

[4S-(4α,12aα)]-4-(diméthylamino)-9-[[2-(diméthylamino)-3,3-diméthyl-1-oxobutyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule I, R = ^{t}Bu, R^1 = H, W = diméthylamino)** ;

[4S-(4α,12aα)]-4-(diméthylamino)-9-[[2-(éthylamino)-2-méthyl-1-oxobutyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène-carboxamide **(Formule I, R = Et, R^1 = Me, W = éthylamino);**

[4S-(4α,12aα)]-4-(diméthylamino)-9-[[2-(diméthylamino)-3-hydroxy-1-oxopropyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule I, R = CH_2OH, R^1 - H, W = diméthylamino)** ;

[7S-(7α,10aα)]-N-[9-(aminocarbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-α-(hydroxyméthyl)-4-méthyl-1H-imidazole-1-acétamide **(Formule I, R = CH_2OH, R^1 = H, W = 4-méthyl-1H-imidazol-1-yle)** ;

[4S-(4α,12aα)]-9-[[2-(diéthylamino)-3-mercapto-1-oxopropyl]amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule I, R = mercaptométhyle, R^1 = H, W = diméthylamino)** ;

[7S-(7α,10aα)]-N-[9-(aminocarbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-α-(mercaptométhyl)-1-pipérazineacétamide **(Formule I, R = mercaptométhyle, R^1 = H, W = pipérazin-1-yle);**

acide [7S-(7α,10aα]-4-[[9-(aminocarbonyl)-7-(diméthyl-amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-amino]-3-(hexylamino)-4-oxobutanoïque **(Formule I, R = carboxyméthyle, R^1 = H, W = hexylamino);**

acide [7S-(7α,10aα)]-5-[[9-(aminocarbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-amino]-4-(cyclopropylamino)-5-oxopentanoïque **(Formule I, R =**

2-carboxyléthyle, R^1 = H, W = cyclopropylamino);

[4S-(4α, 12aα)]-4-(diméthylamino)-9-[[2-(diméthylamino)-2-phénylacétyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène-carboxamide **(Formule I, R = phényle, R^1 = H, W = diméthylamino) ;**

[4S-(4α, 12aα)]-9-[[(butylamino)(4-hydroxyphényl)-acétyl]amino]4-(diméthylamino)-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule I, R = 4-hydroxy-phényle, R^1 = H, W = butylamino);**

[4S-(4α,12aα)]-4-(diméthylamino)-9-[[2-(diméthylamino)-2-(4-méthoxyphényl)acétyl]amino]-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule I, R = 4-méthoxyphényle, R^1 = H, W = diméthylamino) ;**

[4S-(4α,12aα)]-4-(diméthylamino)-9-[[2-(éthylméthyl-amino)-2-[4-(trifluorométhyl)phényl]-acétyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule I, R = 4-trifluoro-méthylphényl, R^1 = H, W = N-éthylméthylamino);** ou

[4S-(4α,12aα)]-4-(diméthylamino)-9-[[[4-(diméthylamino)phényl](2-propénylamino)acétyl]amino]-1,4,4a, 5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule I, R = 4-(diméthylamino)phényle, R^1 = H, W = 2-propénylamino).**

7. Composé qui est un des suivants :

[7S-(7α,10aα)]-N-[9-(aminocarbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-4-éthyl-lH-pyrazole-1-acétamide **(Formule I, R et R^1 = H, W = 4-éthyl-1H-pyrazol-1-yle) ;**

[4S-(4α,12aα)]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-9-[[[méthyl(phénylméthyl)amino]acétyl]amino]-2-naphtacène-carboxamide **(Formule I, R et R^1 = H, W = N-méthylbenzylamino);**

[7S-(7α,10aα)]-N-[9-(aminocarbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-6-méthyl-2-azabicyclo-[2.2.2]octane-2-acétamide **(Formule I, R et R^1 = H, W = 6-méthyl-2-azabicyclo[2.2.2]octan-2-yle) ;**

[4S-(4α,12aα)]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-[[[[(2-méthyl-cyclo-propyl)oxy]amino]acétyl]amino]-1,11-dioxo-2-naphtacènecarboxamide **(Formule I, R et R^1 = H, W = (2-méthylcyclopropyl)oxyamino);**

[7S-(7α,10aα)]-N-[9-(aminocarbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-3-éthyl-1-pyrrolidine-acétamide **(Formule I, R et R^1 = H, W = 3-éthyl-pyrrolidin-1-yle) ;**

[7S-(7a,10aa)]-N-[9-(aminocarbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-4-(aminométhyl)-α-méthyl-1-pipéridineacétamide **(Formula I, R = CH_3, R^1 = H, W = 4-aminométhylpipéridn-1-yle) ;**

bromhydrate de [4S-(4α,12aα)]-4-(diméthylamino)-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-[[2-[[(3-méthylcyclobutyl)oxy]amino]-1-oxobutyl]amino]-1,11-dioxo-2-naphtacènecarboxamide **(Formule I, R = H, R^1 = Et, W = 3-méthylcyclobutyloxyamino);**

[7S-(7α,10aα)]-N-[9-(aminocarbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10, 12-dioxo-2-naphtacényl]-a-éthyl-4-méthyl-2-isoxazolidineacétamide, **(Formule I, R = Et, R^1 = H, W** = 4-méthyl-isoxazolidin-2-yle);

[7S-(7α, 10aα)]-N-[9-(aminocarbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-α-éthyl-3-méthyl-4H-1,2,4-triazole-4-acétamide **(Formule I, R = Et, R^1**

= H, **W = 3-méthyl-4H-1,2,4-triazol-4-yle);**
ou

acide [7S-(7α, 10aα)]-4-[[9-(aminocarbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]amino]-3-[éthyl(phénylméthyl)amino]-4-oxobutanoïque **(Formule I, R = carboxyméthyle, R^1 = H, W = N-éthylbenzylamino).**

8. Composé selon la revendication 3, qui est un des suivants

monochlorhydrate de [4S-(4α,12aα)]-9-[(bromoacétyl)-amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène-carboxamide **(Formule III, R et R^1=H, Y est Br, HCl sel) ;**

monochlorhydrate de [4S-(4α,12aα)]-9-[(chloroacétyl)-amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène-carboxamide **(Formule III, R et R^1=H, Y est Cl, HCl sel);**

monobromhydrate de [4S-(4α,12aα)]-9-[(bromoacétyl)-amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène-carboxamide **(Formule III, R et R^1=H, Y est Br, HBr sel) ;**

monosulfate de [4S-(4α,12aα)]-9-[(bromoacétyl)amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène-carboxamide **(Formule III, R et R^1=H, Y est Br, sel monosulfate);**

monobromhydrate de [4S-(4α,12aα)]-9-[(2-bromo-1-oxopropyl)amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule III, R = CH_3, R^1 = H, Y est Cl, HBr sel) ;**

bromhydrate de [4S-(4α, 12aα)]-9-[(2-bromo-2-méthyl-1-oxopropyl)amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule III, R et R^1 = CH_3, Y = Br) ;**

bromhydrate de [4S-(4α, 12aα)]-9-[(2-bromo-1-oxobutyl)-amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène-carboxamide **(Formule III, R = Et, R^1 = H, Y = Br) ;**

bromhydrate de [4S-(4α, 12aα)]-9-[(2-bromo-1-oxopentyl)-amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène-carboxamide **(Formule III R = Pr, R^1 = H, Y = Br);**

bromhydrate de [4S-(4α,12aα)]-9-[(2-bromo-2-méthyl-1-oxobutyl)amino]- 4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule III, R = Et, R^1 = Me, Y = Br) ;**

bromhydrate de [4S-(4α,12aα)]-9-[(2-bromo-3-hydroxy-1-oxopropyl)amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule III, R = Et, R^1= Me, Y = Br);**

bromhydrate de [4S-(4α, 12aα)]-9-[(2-bromo-3-mercapto-1-oxopropyl)amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule III, R = mercaptométhyle, R^1 = H, Y = Br) ;**

bromhydrate d'acide [7S-(7α, 10aα)]-4-[[9-(amino-carbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10-12-dioxo-2-naphtacényl] amino]-3-bromo-4-oxobutanoïque **(Formule III, R = carboxyméthyl, R^1 = H, Y = Br,);**

bromhydrate d'acide [7S-(7a,10aa)]-5-[[9-(aminocarbonyl)-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octa-

hydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]amino]-4-bromo-5-oxopentanoïque **(Formule III, R = 2-carboxyéthyl, R^1 = H, Y = Br.)**;

bromhydrate de [4S-(4α, 12aα)]-9-[(bromophénylacétyl)-amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène-carboxamide **(Formule III, R = phényl, R^1 = H, Y = Br)** ;

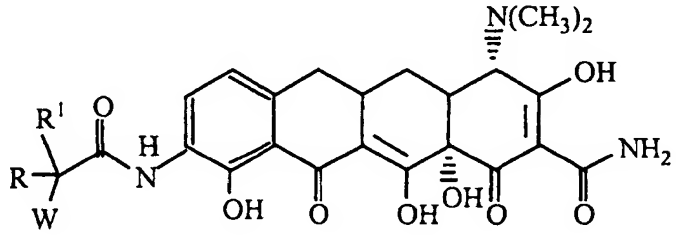
bromhydrate de [4S-(4α,12aα)]-9-[[bromo(4-hydroxyphényl)acétyl]amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule III, R = 4-hydroxyphényle, R^1 = H, Y = Br)** ;

bromhydrate de [4S-(4α,12aα)]-9-[[bromo(4-méthoxyphényl)acétyl]amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule III, R = 4-méthoxyphényle, R^1 = H, Y = Br)** ;

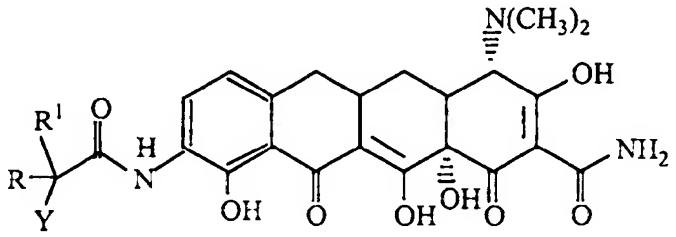
bromhydrate de [4S-(4α,12aα)]-9-[[bromo[4-(trifluorométhyl)phényl]acétyl]amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule III, R = 4-trifluorométhylphényle, R^1 = H, Y = Br)** ;
et

bromhydrate de [4S-(4α,12aα)]-9-[[bromo[4-(diméthylamino)phényl]acétyl]amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide **(Formule III, R = 4-(diméthylamino)phényle, R^1 = H, Y = Br)**.

9. Procédé de production d'un composé, ou de son sel organique ou inorganique ou complexe métallique, de formule :

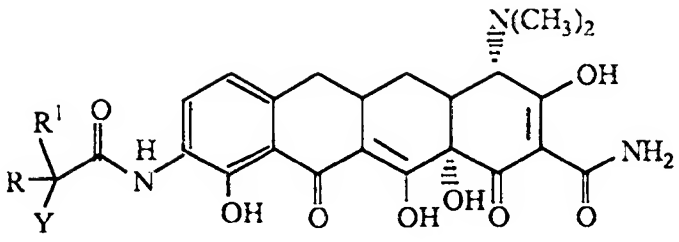


selon la revendication 1, qui comprend la réaction d'une 9-[(haloacyl)amido]-6-déméthyl-6-déoxytétracycline, ou son sel organique et inorganique ou complexe métallique, de formule :

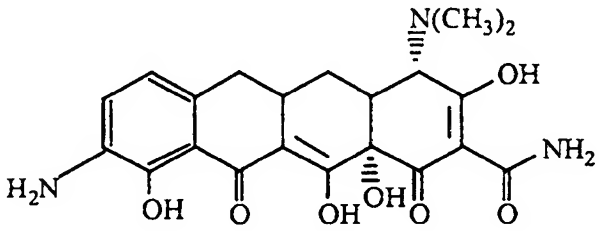


selon la revendication 3, avec un nucléophile de formule WH, dans laquelle W est comme défini dans la revendication 1, dans un solvant polaire aprotique et dans une atmosphère inerte.

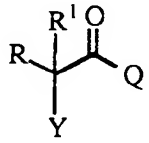
10. Procédé de production d'un composé, ou son sel organique et inorganique ou complexe métallique, de la formule :



selon la revendication 3, qui comprend la réaction de la 9-amino-6-déméthyl-6-déoxytétracycline, ou son sel organique et inorganique ou complexe métallique, de formule :

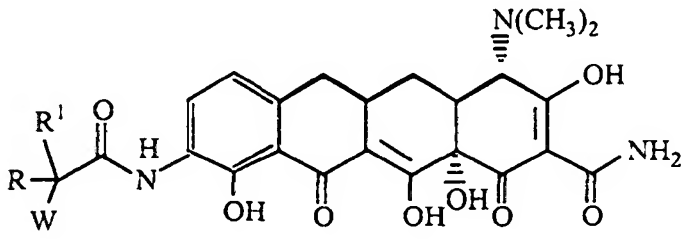


avec un halogénure d'haloacyle en chaîne droite ou ramifiée de formule :

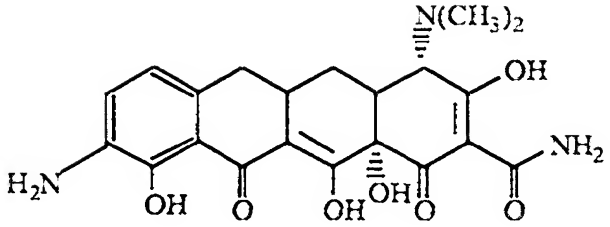


dans laquelle Y, R et R^1 sont comme défini dans la revendication 3 et Q est halogène choisi parmi brome, chlore, iode et fluor, dans un solvant inerte dans un solvant polaire aprotique et en présence d'une base.

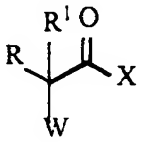
11. Procédé de production d'un composé, ou son sel organique et inorganique ou complexe métallique, de formule :



selon la revendication 1, qui comprend la réaction d'une 9-amino-6-déméthyl-6-déoxytétracycline, ou son sel organique et inorganique ou complexe métallique, de formule :



avec un halogénure d'acide de formule :



dans laquelle R, R^1, et W sont comme défini dans la revendication 1 et X est choisi parmi brome, chlore, iode et fluor, dans un solvant inerte dans un solvant polaire aprotique et en présence d'une base.

12. Utilisation d'un composé selon l'une quelconque des revendications 1, 2, 5, 6 ou 7 dans la préparation d'un médicament pour la prévention, le traitement ou le contrôle d'infections bactériennes chez les animaux à sang chaud.

13. Composition pharmaceutique d'une substance comprenant une quantité pharmacologiquement efficace d'un composé selon la revendication 1, 2, 5, 6 ou 7 en association avec un support pharmaceutiquement acceptable.

14. Composition vétérinaire qui comprend une quantité pharmacologiquement efficace d'un composé selon la revendication 1, 2, 5, 6 or 7 et un support pharmaceutiquement acceptable.